BERKOWITZ'S PEDIATRICS

A PRIMARY CARE APPROACH

Carol D. Berkowitz, MD, FAAP

6th Edition

American Academy of Pediatrics

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Preface

It has been nearly 25 years since the publication of the first edition of what was then simply *Pediatrics: A Primary Care Approach*. That book contained 113 chapters and 500 pages. The section titled Chronic Diseases included HIV, chronic lung disease, and chronic osteomyelitis, conditions no longer included in this current edition. The impetus for the book came from a series of noontime lectures I had given to the residents at Harbor-UCLA Medical Center on topics I wish I learned about during my pediatric residency but only acquired by having my own children and in practice. Most of the authors for the first edition were my fellow faculty.

As we move into the sixth edition, the landscape of pediatrics has continued to change and the book has expanded significantly, with 157 chapters, more than 1,000 pages, and authors from around the United States.

While we have conquered many diseases, particularly infectious ones, other problems have befallen our children. These problems, such as poverty, violence, and exploitation, were no doubt present when the first edition was written, but they certainly weren't center stage on our radars. I am pleased with how we have been able to remain in the forefront of pediatrics, expanding to cover the key issues confronting children, their parents, and their communities in the 21st century and recognizing the changing face of the practice of medicine, be it health systems science or population medicine.

I want to thank all our contributors for the quality of their work and for the recommendations for additional chapters. I also want to acknowledge the suggestions we have received from doctors in other disciplines, including family and emergency medicine and the nurse practitioner community.

The Publishing staff members at the American Academy of Pediatrics are outstanding. Mary Kelly, senior editor, professional and clinical publishing, was a particularly patient editor with the reassuring phrase, "It's all good." Thanks also to Laura Underhile, editor, professional/clinical publishing, and Alain Park for their work on the companion instructor's guide. And to Claudette Hoskins, thanks for your help, patience, and the ability to figure out what was wrong with my computer!

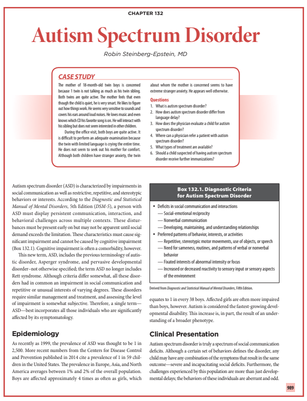
Carol D. Berkowitz, MD, FAAP

Using This Book

For the first time, *Berkowitz's Pediatrics: A Primary Care Approach* has been expanded to a 3-part system that further reinforces the key messages found in the text. The 3 components of this system are

- A *textbook* for use by students and instructors
- An *instructor's guide*
- *Student worksheets*

Together, they form a comprehensive program for students, pediatric residents, pediatric nurse practitioners, pediatric physician assistants, and other health care professionals.

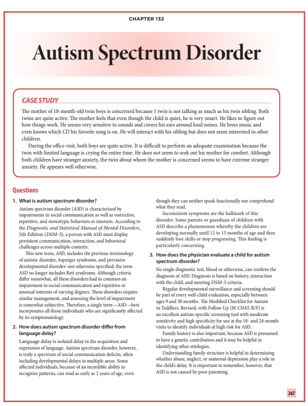


Textbook

The sixth edition of *Berkowitz's Pediatrics: A Primary Care Approach* continues its tradition of providing clear, practice-oriented guidance on the core knowledge in pediatrics. This patient-focused, practical text strives to present users with the situations and challenges they are most likely to encounter in their careers.

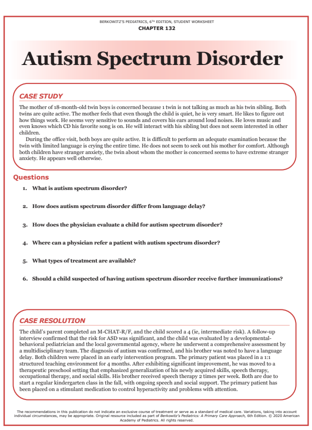
Five new chapters have been added to this edition of the text:

- Health Systems Science
- Population Health for Pediatricians
- Social Determinants of Health: Principles
- Adverse Childhood Experiences: Trauma-Informed Care
- Commercially Exploited Children and Human Trafficking



Instructor's Guide

The newly created *Berkowitz's Pediatrics Instructor's Guide* is designed to help facilitate learner-initiated discussion about core pediatric principles and common pediatric conditions. It also provides answers to the case study questions presented in each chapter of the textbook. The instructor's guide allows for instructor and program flexibility as to how the book and the accompanying questions are used.



Student Worksheets

Student worksheets corresponding to each chapter's case study questions are available online at https://services.aap.org/en/publications/berkowitz/ in a user-friendly format that users can download, complete, and print or email to prepare for discussions. The case study questions contained in the worksheets are designed to help users critically apply the theories presented throughout the textbook. Students will be able to answer all case study questions by reading the corresponding chapter in the text. It is also appropriate to access some of the resources referenced in the chapters.

PART 1

Primary Care: Skills and Concepts

CHAPTER 1

Primary Care: Introduction

Niloufar Tehrani, MD

CASE STUDY

As a primary care physician, you evaluate a 2-year-old boy who is presenting to the office for the first time. The mother states he has always been small; he was born at term but weighed only 2,272 g (5 lb). She is a single mother, and he is her only child. He speaks only 5 words and is quite active. The physical examination is normal, but the boy's height and weight are less than the fifth percentile. The mother reports her son is immunized, but she does not have his immunization records with her at this visit.

Questions

1. What are the 4 components of primary care?
2. What are the main characteristics of a medical home? What are the eligibility criteria for designating a practice as a medical home?
3. What is the difference between a consultation and a referral?
4. Why are laboratory tests done during a routine health maintenance visit?

Primary care is defined as the comprehensive health care a patient receives from the same health professional over a longitudinal period. The term was first used in the 1960s to designate the role of the primary care physician in response to the abundance of subspecialists and lack of generalists among practicing physicians. It is generally accepted that primary care physicians include pediatricians, family physicians, and internists. In 1966, *The Graduate Education of Physicians: The Report of the Citizens Commission on Graduate Medical Education* (the Millis Committee Report) to the American Medical Association recognized the importance of primary care and recommended a national commitment to educating primary care physicians. Primary care was further defined in 1974 by Charney and Alpert, who separated it into component parts: first contact, longitudinal care, family orientation, and integration of comprehensive care. To comprehend the depth of primary care, it is necessary to understand its component parts.

First contact occurs when a patient arrives for medical care at the office of a primary care physician. The visit includes an intake history, complete physical examination, screenings appropriate for age, and an assessment of problems with treatment, if indicated. Of great importance is the establishment of the physician-patient relationship. Physicians become the primary medical resource and counselors to these patients and their families and the first contacts when successive medical problems arise.

Longitudinal care, the second component of primary care, implies continuity of care over time. Physicians assume responsibility for issues concerning health and illness. In pediatrics, such care involves monitoring growth and development, following school progress, screening for commonly found disorders, conducting psychosocial assessments, promoting health, preventing illness with immunizations, and providing safety counseling programs.

Family orientation, the third component of primary care, is a recognition that the provision of adequate care is dependent on viewing patients in the context of their environment and family. In pediatrics, a child's problems become the family's, and the family's problems become the child's. This has become increasingly apparent with the recognition that the social determinants of health (eg, problems of poverty, drug use, obesity, teenage pregnancy, and gang involvement), directly affect a child's health and quality of life (see Chapter 141). The psychosocial forces in a particular child's life are intricately interwoven into that child's health care, and the assessment of these forces is an essential component of the primary care of that child. Environmental exposures (eg, lead contamination of the water supply) have a direct effect on a child's health, and the primary care physician must have knowledge of those environmental threats.

The fourth component of primary care, *integration of comprehensive care*, involves the use of health and educational resources in the community to supplement care as a means of addressing the increased complexity of pediatric medical problems. Primary care physicians integrate and coordinate these services in the best interest of patients. Working with social service agencies, home care providers, educational agencies, and government agencies, physicians can use multiple resources for the benefit of patients. Understanding the available community resources is an important part of a primary care physician's education.

Medical Home

When patients select a primary care physician, they have identified a medical home. The *medical home* incorporates the physical, psychological, and social aspects of individual patients into comprehensive health care services, thus meeting the needs of the whole person. This concept of the medical home was first documented by the American Academy of Pediatrics (AAP) in 1967 in the book *Standards of Child Health Care,* which noted that a medical home should be a central source of all the child's medical records. The

idea of a medical home developed into a method of providing comprehensive primary care and was successfully implemented in the 1980s by Calvin Sia, MD, FAAP, in Hawaii. He is considered to be the "father" of the medical home. In policy statements published in 1992 and 2002 (the latter reaffirmed in 2008), the AAP defined the characteristics of a medical home to be "accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective." Geographic and financial accessibility are key elements in making that home work for patients. The most important aspect of a home, however, is that it be a place in which patients feel cared for.

Since its implementation in pediatrics in 2004, the medical home model was adopted by the American Academy of Family Physicians and the American College of Physicians. The definition of the medical home was expanded to include use of electronic information services, population-based management of chronic illness, and continuous quality improvement. The concept has been accepted as a form of high-quality health care. Cost and quality of benefits have been well documented. Recognizing these benefits, large corporations in collaboration with health professionals formed the Patient-Centered Primary Care Collaborative to promote the idea of designated medical homes. As part of that collaborative, the National Committee for Quality Assurance adopted eligibility criteria for a practice to define itself as a medical home. Requirements for the designation include the adoption of health information technology and decision-support systems, modification of clinical practice patterns, and ensuring continuity of care.

With the advent of health care reform in the United States, as part of the effort to control the rising cost of health care, the federal government has endorsed the concept of the medical home model. The Academic Pediatric Association has defined the *family-centered medical home* to delineate the dependency of the child to the family and community in the medical home model. This principle was highlighted in a consensus statement that was developed and jointly endorsed by the AAP, American College of Physicians, American Academy of Family Physicians, and the American Osteopathic Association.

Role of the Primary Care Pediatrician

As a primary care physician, the pediatrician has a role that has included not only the management of acute illness and injury but also the preventive aspects of well-child care with its focus on immunizations, tracking growth and development, and anticipatory guidance. Currently, there exists a renewed emphasis on the importance of the role of the pediatric primary care physician in assessing the psychosocial aspects of pediatric patients. Evaluation of social issues such as family dysfunction, developmental problems (including learning disabilities) and behavioral problems (including emotional disorders), termed the *new morbidity* by Robert Haggerty, MD, in the 1970s, has become a significant part of the role of the physician. In 1993, the AAP stated that pediatricians are obliged to have knowledge of physical and environmental factors and behaviors affecting health, normal variations of behavior and emotional development, risk factors and behaviors affecting physical health, and behavior problems. The focus of the pediatrician should be detection, evaluation, and management, with referrals if necessary. Newer morbidities secondary to the increasing complexity of our society were outlined in 2001 by the AAP. These include school problems, mood and anxiety disorders, adolescent suicide and homicide, firearms, school violence, drug and alcohol abuse, HIV, obesity, and the effects of the media on children. Other psychosocial factors, such as poverty, homelessness, single-parent families, divorce, working parents, and child care, necessitate that pediatricians work with social service agencies to deliver appropriate care to their patients. The role of the primary care physician is continually expanding in an effort to deliver comprehensive care to each patient in a medical home. This care is often rendered by physician-led teams that include other health professionals.

Subspecialist Care

Considerable advancement has been made in medical knowledge and technology in the past several decades. Total knowledge of all fields is impossible for any individual physician. As a result, the role of the subspecialist physician has developed as an adjunct to that of the primary care physician. New fields of subspecialties, such as child abuse pediatrics, have arisen as a response to increased knowledge. The primary care physician should seek subspecialist consultation when the suspected or known disease process is unusual or complicated, in cases that require the use of specialized technology, and in situations in which the primary care physician has little experience with the disease. Generally, subspecialists evaluate patients and concentrate on the organ system or disease process in their area of expertise.

Use of a subspecialist is termed *secondary care*. The primary care physician can elicit the help of a subspecialist in the form of a consultation or a referral. When initiating a *consultation*, the primary care physician seeks advice from the consultant on workup or management of the patient. The consulting physician assesses the patient with a history and physical examination, focusing on the particular specialty. The consultant recommends possible additional laboratory tests and offers a diagnosis and treatment plan, after which the patient returns to the primary care physician for coordination of further care.

Electronic, abbreviated consultations can now be conducted using an e-consultation system. These consultations give the primary care physician a treatment plan, which may also include 1 or more visits to the subspecialist. For example, an 8-year-old girl with weight loss and persistent abdominal pain has an upper gastrointestinal radiograph series that reveals a duodenal ulcer. Her primary care physician requests a consultation from a pediatric gastroenterologist for an endoscopy to allow definitive diagnosis and up-to-date management guidelines. After the procedure, the girl returns to the primary care physician with recommendations for treatment and further care.

Primary care physicians can also generate a referral to a subspecialist, which differs from a consultation. A *referral* requests that the subspecialist assume complete care of the patient. This transfer of

care may be to a tertiary care site where a subspecialist provides care and assumes responsibility for coordinating further patient care. For example, a 4-year-old boy with recurrent fever, hepatosplenomegaly, and blasts on peripheral blood smear is referred to a pediatric oncologist for diagnosis, treatment, and ongoing medical care.

When requesting advice from subspecialists, whether on a consultative or referral basis, the primary care physician should outline specific questions with a probable diagnosis to be addressed by the subspecialist. For example, a consultation requesting evaluation of a child with hematuria is inappropriate. The primary care physician should perform a basic diagnostic evaluation and suggest the most likely diagnosis, after which the child can be referred appropriately. For example, a child with a diagnosis of nephritis should be sent to a pediatric nephrologist, whereas a child with a diagnosis of Wilms tumor should be sent to a pediatric oncologist.

When primary care physicians and subspecialists function cooperatively and offer 3 levels of care (ie, primary, referral, consultative), patients receive the highest quality medical care. Generally, care provided by subspecialists is characterized as being more expensive and procedure driven. Subspecialists order more laboratory studies than primary care physicians, which further inflates the cost of medical care. Additionally, if a patient lacks longitudinal health care and sees multiple practitioners, often repeat laboratory studies are ordered. Compared with subspecialty care, primary care is believed to deliver more cost-effective medical care. The spiraling cost of medical care has resulted in continued nationwide emphasis on producing more primary care physicians. It should be remembered, however, that the subspecialist plays an essential supplementary role to the primary care physician when managing complicated diseases. A balance between generalists and subspecialists must be maintained in the education process.

Laboratory Tests

For most conditions, the diagnosis is revealed by the history and physical examination in more than 95% of cases. Thus, good communication skills are a basic tenet of primary care. Patients frequently complain about unnecessary laboratory tests, which increase the cost of medical care, and the prescription of unnecessary medications. To lessen these problems, the primary care physician should be discriminating when ordering laboratory tests and prescribing medications, recognizing their value as well as their potential iatrogenic effects.

In primary care, laboratory tests are used to help confirm a condition suspected on the basis of the history or physical examination or diagnose a condition that may not be apparent after a thorough history and physical assessment. In pediatrics especially, the value of each test result should be weighed against the inconvenience, discomfort, and possible side effects in children. Tests in at-risk children can also be used as screening tools to prevent disease or identify a disease early so that treatment can begin and symptoms can be minimized. Laboratory studies can provide a host of other information, including data to establish a diagnosis, knowledge necessary to select therapy or monitor a disease, and information about the risk of future disease. Organ function, metabolic activity, and nutritional status also can be assessed, and evidence of neoplastic or infectious disease can be provided. Additionally, laboratory studies can be used to identify infectious and therapeutic agents or poisons.

Screening laboratory tests are used when the incidence of an unsuspected condition is sufficiently high in a general population to justify the expense of the test (see Chapter 13). Subclinical conditions, such as anemia, lead poisoning, and hypercholesterolemia, are part of some health maintenance assessments.

Physicians must remember that variability exists in test results and that laboratory error can occur. Laboratory results should always be viewed in the context of the patient. The sensitivity of a test, the ability of the test to detect low levels, and the specificity of a test for the substance being measured must also be considered by the physician when evaluating a test result.

Challenges for the Future

The role of the primary care physician in health care delivery has increased in importance. In 2010, the Patient Protection and Affordable Care Act was signed into law. This law emphasizes the importance of the medical home and promotes its implementation. Two of the basic tenets of primary care—accessibility and an ongoing relationship with the primary care physician, both of which are reported by patients to be very important—are recognized as essential components of the medical home. The challenge continues to ensure continuity in health care funding to preserve the continuity of the medical home. Payment reform promises to improve payment to primary care practices and rewards high performance. As proposed in health care reform, through accountable care organizations, primary care physicians would be the foundation of the organization whose mission is management of the continuum of care and cost as well as ensuring quality of care.

Access to same-day care, which is part of the obligation of the medical home and essential to pediatric patients, can be difficult in the busy schedule of primary care physicians. Practices must accommodate these visits. Community health centers can provide excellent medical homes for children in families with low income; however, these centers can have challenges with accessibility and adequate referral sources. Walk-in immediate medical care clinics and retail clinics have arisen, but episodic visits in a variety of settings do not deliver comprehensive care for the patient, and these short visits may not take into account the entirety of the patient's medical history. This creates a challenge for the primary care physician and medical home to develop a system to integrate the information from these encounters into the comprehensive medical record.

With the advent of hospitalists providing inpatient care, primary care physicians may not be included in inpatient management, which can make it challenging for primary care physicians to retrieve important information about the care of their patients.

Medical care reform incorporates accountability, demonstration of quality of care, and standards of medical practice into the medical home model, which has resulted in an exponential increase in the

oversight and bureaucracy of medical care. This business of medicine with redundant oversight of medical care has placed a tremendous burden of administrative activities on the primary care physician. Physicians face a significant challenge in providing care while answering to administrative structures. Additionally, although the use of electronic medical records decreases some of the challenges of information retrieval and communication among medical providers, it poses other challenges in a potential lack of pediatric functionality and loss of productivity.

The biggest challenge for pediatric primary care physicians has always been to ensure the future of health care funding to provide all children access to and availability of a medical home. The Patient Protection and Affordable Care Act aims to provide health coverage for nearly all children, but in a multipayer, market-driven health care system, significant challenges will remain. A multitude of programs exist to pay for children's health care, and these programs vary by state. Families move among payers, which disrupts continuity of care. Universal health care for children is being advocated. Without a secure national plan for financing, children's health care will continue to be variable, resulting in disparities in children's health.

CASE RESOLUTION

You ask the mother about her son's former physician and obtain signed permission to get the prior medical records, including immunizations. You attempt a hearing assessment as the initial step in evaluating his speech delay, but the patient does not cooperate. You ask the mother about access to food and complete a referral to the Special Supplemental Nutrition Program for Women, Infants, and Children and provide her with information about the Supplemental Nutrition Assurance Program (ie, food stamps). You provide the patient with an age-appropriate book from Reach Out and Read and make a return appointment for 1 month hence to continue care and determine whether the patient needs any immunizations.

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CHAPTER 2

Talking With Parents

Geeta Grover, MD, FAAP

CASE STUDY

An 8-month-old boy with a 1-week history of cough and runny nose; a 2-day history of vomiting, diarrhea, and fever; and a temperature of 38.3°C (101°F) is evaluated in the emergency department (ED). The mother is very concerned because her son's appetite has decreased, and he has been waking up several times at night for the past 2 days.

A nurse interrupts and says that paramedics are bringing a 5-year-old trauma victim to the ED. The appearance of the 8-month-old child is quickly assessed; he seems active and alert. Bilateral otitis media is diagnosed. Before leaving the examination room the physician says to the mother, "Your son has a viral syndrome and infection in his ears. I am going to prescribe an antibiotic that you can begin giving him today. Give him ibuprofen as needed for the fever. Don't worry about his vomiting and diarrhea; just make sure that he drinks plenty of liquids and don't give him milk or milk products for a few days. Bring him back here or to his regular doctor if his fever persists, he doesn't eat, he has too much vomiting or diarrhea, he looks lethargic, or if he isn't better in 2 days."

Questions

1. How much information can most parents absorb at one time? Did this mother receive more information than she can reasonably be expected to remember?
2. How do you assess parental concerns? Did the physician sufficiently address the mother's worries?
3. How do you know whether a parent has understood all the information? Was this mother given a chance to clarify any questions she had?
4. What are some barriers to effective doctor-parent communication?
5. How does the setting itself influence communication?

Communication is the foundation of the therapeutic relationship between physicians, patients, and patients' families. Effective communication in the pediatric setting involves the exchange of information between physicians, parents, and children. In addition, observing the interaction between parents and children gives physicians an opportunity to assess parenting skills and the dynamics of the parent-child relationship. The communication needs of parents and children are quite different, which makes the exchange of information challenging. Parental concerns should be addressed in a sensitive, empathetic, and nonjudgmental manner. A nonthreatening, pleasant demeanor and age-appropriate language help facilitate communication with children (see Chapter 3).

Pediatrics encompasses not only the traditional medical model of diagnosis and treatment of disease but also maintenance of the health and well-being of children through longitudinal care and the establishment of ongoing relationships between physicians and families. Personal relationships between physicians and families create an atmosphere in which information can be exchanged openly. The pediatrician's role in such relationships is to not only diagnose and treat but also to listen, advise, guide, and teach.

The doctor-patient relationship is truly a privilege. Patients entrust physicians with their innermost thoughts and feelings, allow them to touch private parts of their bodies, and trust them to perform invasive procedures or administer medications. Mutual respect is essential for the development of a healthy relationship between physicians, parents, and children. Through practice and continued awareness of interpersonal abilities, the physician can develop good communication skills. All physicians eventually develop their own personal interviewing and examination style. What seems awkward and difficult at first soon becomes routine and even enjoyable as the physician becomes more comfortable with patients and their families.

Parental Concerns

Parents' preconceived ideas and concerns about their children's illnesses can greatly influence the exchange of information between physicians and parents. At health maintenance or well-child visits, it is important for the pediatrician to address parents' nonmedical and psychosocial concerns, such as their children's development, nutrition, and growth. Often these questions stem from discussions with other parents or, increasingly, from information received from various online and media resources (see Chapter 7). Although such concerns may seem trivial to the pediatrician, they may be extremely important to parents. In addition to addressing the needs of the child, the health maintenance visit also affords the pediatrician an opportunity to assess and address parental needs. Parental depression, substance abuse, family violence, or marital discord all can have profound effects on children's health and development. Similarly, the conditions in which children and their families live,

learn, work, and play can affect both physical and emotional health. Collectively, these conditions are known as the *social determinants of health* (see Chapter 141).

When evaluating children brought in for illness, it is important to ask parents what concerns them most. Parental fears may be much different from medical concerns. Failure to give parents the opportunity to ask questions or to address these concerns in a sensitive manner may result in dissatisfaction and poor communication.

The Pediatric Interview

Pediatric interviews are conducted in a variety of settings for many different reasons. The first interaction between the physician and parent or parents may be during the prenatal interview before the birth of the child, in the hospital following the delivery, or in the doctor's office during the well-baby visit. Later, the physician may see a child in the office for regular health maintenance visits or in the office, emergency department (ED), or hospital for an acute illness.

The specific clinical situation dictates the information that must be gathered and the appropriate interviewing techniques. During the prenatal visit, the physician should discuss common concerns and anxieties about the new baby with the prospective parent or parents. In addition, the prenatal visit affords the parent or parents an opportunity to interview physicians and evaluate their offices and staff.

In the emergency setting, the physician must elicit pertinent information necessary to make decisions about management within a short period. Lack of a long-term relationship can make communication in the ED particularly challenging. The physician should mostly use focused, closed-ended questions in this setting. For the periodic health maintenance visit, however, the use of broad, open-ended questions is more appropriate, and closed-ended questions should be used only as necessary for clarification.

Communication Guidelines

Professionalism encompasses technical, intellectual, and humanistic competencies. Clinicians are increasingly seeing conditions that may not be treatable; however, that does not mean the clinician cannot provide healing. Whereas "treatment" focuses on cure, "healing" is about building relationships with patients and helping them optimize emotional and physical health so that they may continue to pursue what has meaning and value for them.

Overall principles that are applicable regardless of the setting include interacting with the child and family in a professional yet sensitive and nonjudgmental manner. Common courtesies, such as knocking before entering the room, dressing and behaving in a professional manner, introducing oneself, and addressing parents and children by their preferred names, are always appreciated and welcomed. Taking a few moments to socialize with families develops a more personal relationship that may allow more open conversation about sensitive and emotional issues.

Family-centered care is an approach to health care in which the physician realizes the vital role that families play in ensuring the health and well-being of children. Physicians who practice family-centered care convey respect for parents' insight into and understanding of their children's behavior and needs, and actively seek out their observations and incorporate their family preferences into the care plan as much as possible. Benefits of family-centered care include a stronger alliance between the physician and family; increased patient, family, and professional satisfaction; and decreased health care costs. Since the passage of the Health Information Technology for Economic and Clinical Health (HITECH) Act in 2009, the electronic medical record (EMR) is increasingly affecting the practice of medicine (see Chapter 6). Although the EMR has the potential to improve patient understanding of health information as well as to improve sharing of medical information, without conscious effort to adjust clinical speaking and documentation practices, this new model of practice may also negatively affect patient-centered communication. Some behaviors that facilitate patient-centered communication with the EMR include screen-sharing, cessation of typing during sensitive discussions, and maintaining eye contact or continuing to speak while typing. In this digital age, physicians are learning to listen, talk, think, and type simultaneously.

The medical visit may be divided into 3 parts: the interview, physical examination, and concluding remarks. Examples of doctor-parent and doctor-child communications for each of these components are provided in Table 2.1.

Interview

The goal of the interview is to ascertain the chief concern, determine appropriate medical history, and gain an understanding of the family's perspective of the illness or its specific concerns. It is important to address cognitive (ie, informational) and affective (ie, emotional) needs of the family during the interview. The interview usually begins with open-ended questions to give parent and child an opportunity to discuss their concerns and outline their agenda for the visit. Often, the real reason for the visit is not disclosed until the family believes the physician to be trustworthy and honest. Rachel Naomi Remen, MD, coined the term *generous listening* to describe a technique of receiving and respecting information without judgment or any agenda to analyze it and determine what to do next. Generous listening creates a space of safety that allows parents and children to say what they perceive to be true. After issues have been laid out, closed-ended questions can be used to clarify and further define the information presented. It often becomes necessary to guide the interview, especially when parents have several broad issues on their agenda for that visit and time does not permit discussion of them.

The physician should gently acknowledge parental concerns and define time limitations. These actions allow the physician to focus on the most salient issues of that visit. Additionally, the physician should limit the use of medical jargon (ie, scientific terms) and be aware of nonverbal communication. A sincere, empathic, and compassionate communication style helps parents feel truly understood even if the physician can do little to help the situation. Pauses and periods of silence should be used, especially when discussing emotionally difficult issues, to convey to parents and children

Table 2.1. Communication Guidelines and Techniques for the Pediatric Medical Visit

Component of Medical Visit	*Technique*	*Examples*
Interview	Open-ended questions.	"How is Susie?"
	Closed-ended questions.	"Does she have a cough?"
	Repetition of important phrases.	"She has had a high fever for 4 days now?"
	Reflective listening.	"It sounds like you are concerned that this may be serious."
	Clarification.	"What do you mean by, 'Susie was acting funny'?"
	Pauses and periods of silence.	"I see that it is difficult for you to talk about this. Take your time."
	Limit medical jargon.	"Susie has an ear infection" vs "Susie has otitis media."
	Guide the interview.	"Right now, I am most interested in hearing about the symptoms of this illness."
	Be aware of nonverbal communication.	Use eye contact and phrases such as "I see."
	Acknowledge parental concerns.	"Worrying about hearing loss is understandable."
	Empathize.	"A temperature of 104°F can be very frightening."
	Remember common courtesies.	Knock before entering.
	Recognize personal limitations.	"I am not an expert in this area. I would like to consult with a colleague."
	Summarize.	"So, she has had fever for 4 days, but the rash and cough began 1 week ago?"
Physical Examination	Show consideration for the child.	"It's OK to be afraid."
	Inform.	"That took me some time, but her heart sounds normal."
	Explain procedures.	"You may feel a little uncomfortable during the rectal examination."
	Avoid exclamations.	"Wow! I have never seen anything like this!"
Concluding Remarks	Provide closure.	"Our time is over today. May we discuss this at the next visit?"
	Minimize discharge instructions.	"Call me if her rash recurs."
	Be specific.	"I am going to treat her with amoxicillin" vs "I'll prescribe an antibiotic."
	Praise and positive feedback.	"You're doing a great job."
	Confirm parental understanding.	"Please repeat for me Susie's diagnosis and treatment instructions so I'm sure I've been clear in explaining them to you."
	Give the parent or parents permission to ask questions.	"Please feel free to ask me about anything that concerns you."
	Reassurance.	"I know you are worried about her high fever, but I can reassure you that the fact she is playful and hungry are both good signs."

that their physician cares enough to listen. Physicians should not underrate their own knowledge; however, they should recognize their limitations and use consultants appropriately. Finally, the physician's understanding of the chief concern and history should be summarized so that the parent or parents have an opportunity to clarify points of disagreement.

The primary care physician faces increasing demands to address not only the physical but also the psychosocial health needs of patients. *Patient-centered care* is a comprehensive approach to medical care that encourages communication between the physician, patient, and family. The clinician addresses the immediate pressing medical concerns in the context of each patient's unique environmental circumstances and underlying psychosocial concerns, both of which may directly or indirectly affect health-related outcomes. Empathy, unconditional positive regard, and genuineness are essential physician characteristics in this collaborative approach.

Motivational interviewing is one such patient-centered, collaborative, and directive interaction style that offers an effective means of addressing these developmental, behavioral, and social concerns within the context of a primary care setting. *Motivational interviewing* addresses the ambivalence and discrepancies between a person's current values and behaviors and the person's future goals. In contrast to more traditional medical approaches that rely primarily on authority and education, motivational interviewing is a collaborative approach that relies on eliciting the patient's ideas about change. The physician who practices motivational interviewing understands that trying to move beyond a patient's readiness to change is likely to increase that patient's resistance to treatment; for example, lecturing to an adolescent who is not yet ready to quit smoking about the dangers of smoking is unlikely to be effective and may even produce more resistance. Motivational interviewing requires that the physician follow the 4 principles listed in Table 2.2.

Table 2.2. Principles of Motivational Interviewing

Principle	*Example*
Express empathy.	Use reflective listening.
Identify discrepancy between patient's current behavior and treatment goal.	Patient, not physician, presents arguments for change.
Decrease the likelihood of evoking patient resistance.	Avoid arguing for change.
Support the patient's self-efficacy.	Patient's own belief in the possibility of change is an important motivator.

Derived from Miller WR, Rollnick S. *Motivational Interviewing: Helping People Change.* 3rd ed. New York, NY: Guilford Press; 2013.

Operationally, open-ended questions (eg, "How do you feel about smoking?"), affirmations (eg, "You are tired of having to monitor your blood sugar every day and stick to your diet."), and reflective listening (eg, "You are worried about your daughter's behavior and are concerned that if it persists, she may be expelled from school.") are important tools of motivational interviewing. In addition, physicians who practice motivational interviewing ask permission before giving advice (eg, "Would it be OK if I shared some information with you?"). Alternatively, the physician may state the facts but let the parent interpret the information (eg, "What does this mean to you?"). Research has also shown motivational interviewing to be an effective tool for use with adolescent patients to increase self-efficacy to enact change (eg, adolescent smoking cessation).

Physical Examination

Parents keenly observe physicians' interactions with their children during the examination. It is an important time for the physician to build a therapeutic relationship with the child (see Chapter 3). The transition between the history and physical examination can be made by briefly telling the child and parent what to expect during the examination. The physician should show consideration for the child's fears. In general, physicians often find it helpful to speak with families at periodic intervals during the examination about their observations. Prolonged periods of silence as the physician listens or palpates may be anxiety provoking for the family. Physicians should explain any procedures that they or their staff are going to perform at a level that is appropriate for parents and children. In addition, the physician should try to avoid exclamations or comments to self during the examination (eg, "Wow, that's some murmur!"), which may be alarming to the family.

Concluding Remarks

The conclusion of the visit, which is all too easy to rush through, is extremely important. Closure can be provided by summarizing the diagnosis or outlining plans for a follow-up visit. The parent or parent should be asked to participate by acknowledging closure and helping to develop a management plan. Shared decision making and a consumer model are replacing the traditional paternalistic medical model in which the physician decided what should be done and the patient accepted the recommendations without question. In this shared decision making model, it is important to assess parental readiness for knowledge (especially in emotionally difficult situations) and keep family resources and limitations in mind. Discharge instructions should be minimized, the physician should be specific, and the number of diagnoses, medications, and "as needed" instructions (ie, indications for seeking medical advice, such as "return as needed for high fever") should be limited. When complicated discharge instructions are given, additional physician time may be required to ensure parental understanding. Praising parents on care of their children can boost their self-esteem and confidence and may minimize calls and questions. Parental understanding should be confirmed; parents should be asked to repeat the diagnosis and treatment plan. Simply asking parents if they have understood is not enough because they often say "yes" out of respect for the physician's time or embarrassment that they have not understood what has been said. For example, the physician could say, "I want to be sure that I've spoken clearly enough. Please repeat for me [child's name] diagnosis and treatment instructions."

Barriers to Effective Communication

Barriers to effective communication can be divided into systems-related barriers and interpersonal barriers (Table 2.3). The primary systems barriers are the setting itself and lack of continuity of care. Because of access problems within the health care system (ie, lack of health insurance coverage), many children receive only episodic care from different physicians in acute care clinics or EDs. Without the benefit of long-term relationships, doctor-patient communication may suffer.

Interpersonal barriers include physician time constraints, frequent interruptions, and cultural insensitivity. Frequent interruptions or apparent impatience on the part of the physician conveys to parents and children that the physician does not care or is too busy for them. Language differences may pose

Table 2.3. Barriers to Effective Communication

Barrier Category	*Specific Type of Barrier*	*Example*
Systems	Lack of continuity of care	Episodic care that is primarily illness driven
	The setting itself	Emergency departments and acute care clinics
Interpersonal	Physician time constraints	Appearing impatient or preoccupied
	Frequent interruptions	Pager goes off or asked to come to the telephone
	Cultural insensitivity	Suggesting treatments that are not acceptable within the family's belief systems

a significant barrier, depending on the region in which the physician practices. Ideally, physicians themselves should be able to speak directly with parents and children. If translators are needed, children must not play this role because doing so places them in an awkward situation. Parents of other patients must not be used either, because doing so would violate the patient's privacy. Only professional translators are recommended. Physicians should be sensitive to cultural differences (eg, issues about sex and gender, views on illness, folk remedies, beliefs). Suggesting treatments that are not culturally acceptable or are contrary to folk wisdom simply decreases compliance with prescribed treatment plans. For example, many Eastern cultures believe in the concept of "hot" and "cold" foods and illnesses. Suggesting to a mother that she feed primarily "hot" foods to a child she believes to have an illness that is also "hot" may not be acceptable to her. Such information is rarely volunteered and must be elicited through culturally sensitive patient interviewing.

Not only is effective communication essential for accurate diagnosis, but it is also correlated with improved patient recall of instructions and adherence to prescribed courses of treatment. Poor communication can have negative consequences for the patient (eg, compromised care) and physician (eg, medicolegal consequences). Effective communication enhances medical outcomes and patient satisfaction.

CASE RESOLUTION

The doctor-patient interaction presented in the case study illustrates several of the "not to" points discussed herein. The physician did not acknowledge parental concerns or make sure that the mother had understood the diagnosis and treatment plan. The mother was presented with more information than she could have reasonably been asked to remember. This interaction could have been improved had the physician conveyed to the mother that her concerns were appreciated and reassured her that her child was going to be all right. Furthermore, the physician should have told the mother the name and dosage schedule of the antibiotic to be prescribed and limited the number of "as needed" instructions.

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CHAPTER 3

Talking With Children

Geeta Grover, MD, FAAP

CASE STUDY

The moment you walk into the examination room, the 2-year-old girl begins to cry and scream uncontrollably. She clings to her mother and turns her face away. The mother appears embarrassed and states that her daughter reacts to all physicians this way. After reassuring the mother that you have received such welcomes before, you sit down at a comfortable distance from the girl and her mother. You smile at the girl and compliment her on her dress, but she does not seem to be interested in interacting with you at this point. You place an age-appropriate book on the examination table, indicating to the child that the book is for her. You begin your interview with the mother and try not to look at the girl. Out of the corner of your eye, you see that her crying is easing and she has begun to examine the book you had placed on the table.

Questions

1. How does the age of children influence their understanding of health and illness?
2. Should physicians speak directly with children about their illnesses?
3. At what age can children begin to communicate with physicians about their illnesses?
4. How can older children be involved in the management of their health?
5. How can positioning and placement of children in the examination room affect the overall tone and quality of the visit?

Effective communication is essential in developing a meaningful and trusting relationship with children. In pediatrics, interviewing involves balancing the needs of parents and children. Whereas parents may be more focused on issues pertaining to disease, treatment, or aspects of parenting, children look to physicians with different needs and concerns, depending on their age. Developmental maturity, cognitive level, language ability, and sociocultural factors all play a role in a child's ability to communicate and affect their concepts of health and illness. As children grow and develop, their understanding of health and illness matures and develops as well. Developmentally sensitive communication helps build a trusting relationship that allows pediatricians to guide children as they grow to make appropriate decisions about their own health as well as assume responsibility for behaviors that may affect their health and well-being. The American Academy of Pediatrics advises that physicians have both a moral and an ethical obligation to discuss health and illness with children, and further, in keeping with their developmental capacities, allow them to be active participants in their own care.

Developmental Approach to Communicating With Children

Childhood is a time not only of considerable physical growth but also of tremendous social, emotional, and cognitive maturation. An appreciation of the cognitive stages of development helps pediatricians develop a healthy relationship with their patients by allowing them to communicate with children in an age-appropriate manner. Piaget defined 4 stages of cognitive development, which occur in the same sequence but not at the same rate in all children (Table 3.1).

In the *sensorimotor stage* (birth–2 years of age), children experience the world and act through sensations and motor acts. They are developing the concepts of object permanence, causality, and spatial relationships. In the *preoperational stage*, (2–6 years of age), children understand the world only from their own viewpoint. As egocentric thinkers, they are unable to separate internal from external reality, and fantasy play is important. School-age children (6–11 years of age) are capable of *concrete operational thinking*. These children can reason through problems that relate to real objects. Older children (>11 years of age) have the capacity for abstract thought, which defines the *formal operations* stage.

Table 3.1. The Four Stages of Cognitive Development According to Piaget

Age[a]	Stage	Characteristics
Birth–2 years	Sensorimotor	Experiences the world through sensations and motor acts
2–6 years	Preoperational	Egocentric thinking Imitation and fantasy play
6–11 years	Concrete operational	Mental processes only as they relate to real objects
>11 years	Formal operations	Capacity for abstract thought

[a] Approximate ages.

An appreciation of how children's cognitive development affects their understanding of illness and pain aids physicians in developing therapeutic relationships with their patients. When using a developmental approach to children's understanding of illness, children's explanations of illness are classified into 6 categories that are consistent with Piaget's cognitive developmental stages (Table 3.2). Children 2 to 6 years of age view illness as being caused by external factors near the body (ie, phenomenalism, contagion). Young children engage in so-called magical thinking; proximity alone provides the link between cause and illness. Children 7 to 10 years of age should be able to differentiate between self and nonself. At this stage, they begin to understand that although illness may be caused by some factor outside the body, illness itself is located inside the body (ie, contamination, internalization). Children 11 years of age and older understand physiologic and psychophysiologic explanations of illness.

A similar developmental sequence applies to children's understanding of pain. Younger children may attribute pain to punishment for some transgression or wrongdoing on their part. They may not understand the relationship between pain and illness (eg, "Pain is something in my tummy."). Children with concrete operational thought can appreciate that pain and illness are related, but they may not have a clear understanding of the causation of pain (eg, "Pain is a feeling you get when you are sick."). Older children and adolescents begin to understand the complex physical and psychologic components of pain. For example, they realize that although the bone in the arm is broken, pain is ultimately felt in the head (eg, "Pain goes up some nerves from the broken bone in my arm to my head.").

Guidelines for Doctor-Child Communication

A developmental framework that accounts for children's language skills and causal reasoning abilities is essential in providing appropriate health care to children. Successful communication with children depends not only on spoken words but also on nonverbal cues and the environment itself. A pleasant, child-friendly environment with bright colors, age-appropriate wall decorations, and toys helps make children feel more comfortable. Health professionals should be sincere, because children are extremely sensitive to nonverbal cues. The pediatrician should take a few minutes to enjoy time with the child; this not only gives the child a chance to evaluate the physician but also allows the clinician to begin assessing areas of development. A general principle of the pediatric examination is to begin with the least invasive portions of the examination (eg, heart, lungs, abdomen) and save the most invasive for last (eg, oropharynx, ears). Pediatricians should maintain their self-control in difficult situations. If they approach their limit, they should step outside for a few minutes or ask someone for assistance. Guidelines for physician-child communication are provided in Box 3.1. Age-specific guidelines exist for children from birth to 6 months of age, 7 months to 3 years of age, 3 to 6 years of age, 7 to 11 years of age, and 12 years and older.

Birth to 6 Months of Age

Newborns and infants through 6 months of age have not yet developed a fear of strangers and can therefore usually be easily examined in a parent's arms or on the examination table. Although verbal interaction is limited, it is important to play with newborns and infants, hold them, and talk to them. By watching physicians interact with their infants, new parents have an opportunity to learn how to behave with their infants.

Seven Months to 3 Years of Age

Infants and children 7 months through 3 years of age are perhaps the most challenging with whom to develop rapport and on whom to perform examinations. After entering the examination room, pediatricians should take a few moments to converse or play with these infants and children. Such actions help put children at ease and allow them to get to know their doctor. Children 1 to 2 years of age

Table 3.2. Children's Concepts of Illness

Stage of Cognitive Development	*Age*	*Concept of Illness*	*Question*	*Example of Child's Answer*
Preoperational	2–6 years	Phenomenism	How do people get colds?	"From the sun."
		Contagion	How do people get colds?	"When someone else gets near them."
Concrete Operational	7–10 years	Contamination	How do people get colds?	"You're outside without a hat and you start sneezing. Your head would get cold—the cold would touch it—and then it would go all over your body."
		Internalization	How do people get colds?	"In winter, people breathe in too much air into their nose and it blocks up the nose."
Formal Operations	≥11 years	Physiologic/psychophysiologic	How do people get colds?	"They come from viruses, I guess."
			How do people get a heart attack?	"It can come from being all nerve-racked. You worry too much, and the tension can affect your heart."

Adapted with permission from Biblace R, Walsh ME. Development of children's concepts of illness. *Pediatrics.* 1980;66(6):912–917.

Box 3.1. Physician-Child Communication

Do

- Provide a pleasant environment.
- Pay attention to nonverbal cues.
- Be sincere and honest.
- Enjoy interacting with the child.
- Speak to the child in an age-appropriate manner.
- Get down to the child's eye level.
- Examine from least to most invasive.
- Respect the child's privacy.
- Maintain self-control.
- Have a sense of humor.

Don't

- Limit the child's participation.
- Threaten the child.
- Compare the child to others.
- Engage in power struggles.

will likely busy themselves exploring the room during the history taking. By acknowledging them periodically, physicians build rapport that will help later during the examination. Children 2 to 3 years of age are usually very apprehensive of the examination. The physician should get down to children's eye level when speaking to them. If applicable and true, reassurances such as, "You're not going to get any shots today," can help alleviate their fears. Making false promises, however, can be detrimental to developing a trusting relationship. Because stranger anxiety has developed, the physician should try to do as much of the examination as possible with the child in the parent's lap. Distractions such as stethoscope toys, flashing penlights, or keys may be helpful.

Three to 6 Years of Age

Children's expressive capabilities are growing at tremendous rates during this period. Children can usually be engaged in conversation. Although they should be given repeated opportunities for participation, they should not feel pressured to take part. Children may doubt the physician's true intentions and will likely speak only after their comfort level has been achieved. One way to involve children in the examination is to ask simple questions about their illness (eg, "Where does it hurt?"). In addition, children should be given some control during the examination (eg, "Should I look in your mouth next or your ears?"), and they may be allowed to handle or inspect physicians' equipment when possible. Knowing what to expect next and having some control over the examination can help decrease children's fear and increase their cooperation.

Seven to 11 Years of Age

Making a conscious effort to involve children in this age group in all phases of their care, from gathering data to developing a care plan, can be rewarding because children in this age group are increasingly able to be partners in their care. The physician should make a point of speaking directly with children and not just with parents concerning the chief symptom and history. Pediatric encounters are usually dominated by parents, but the clinician can encourage children to speak by addressing them by name or directing eye gaze toward them. Children can usually provide a good history of their illness, although their concept of time may be misleading. For example, a "long, long time" may mean hours, days, or months, and parents need to clarify this. Children should be asked about school, friends, and favorite activities. Answers to such questions give the physician an idea of children's social and emotional well-being, which may be affecting their physical health. Physicians sometimes overlook children's need for privacy at this age. Drapes should be used appropriately during the examination, and the physician should be sensitive to the presence of other children or adults in the room.

Physicians should begin to involve older children in the management of their illness. Children's understanding of their illness and its management should be assessed (eg, children with asthma could be asked, "What is this inhaler for? When are you going to use it? Show me how."). Children should be given an opportunity to express their fears and anxieties, and these concerns should be discussed (eg, "Asthma can be scary, especially when you can't catch your breath. Have you ever felt like that? Tell me about it."). Children should be involved in the management of their illness, which allows them to develop a sense of responsibility for their own health and medical care. Active participation in their health care visits results in greater visit satisfaction, knowledge, and competence of prescribed medical therapies.

Age 12 Years and Older

Communication with adolescents is discussed in detail in Chapter 4.

Children and Health Literacy

Health literacy (see Chapter 34) is a person's ability to receive, understand, and use information to make appropriate health decisions. At what age does an individual become responsible for his or her own health? Although in the medical setting children often have limited involvement in medical decision making about their own health, in the community children are routinely making decisions that affect their well-being. For example, a 4-year-old chooses water instead of a soda at a friend's birthday party; a 6-year-old runs home to put on her helmet before she rides her neighbor's new bike; an 8-year-old recognizes that her cough is the first sign of an impending asthmatic attack and goes to the school nurse to use her inhaler; or a 12-year-old refuses the cigarette she is being offered. Health attitudes and behaviors learned during childhood affect adult lifestyle choices and thereby health. Health literacy skills should be encouraged from a young age. If information is presented in an age-appropriate manner, children between ages 3 and 18 years are capable of understanding and using health information. In today's world of patient-centered care and ever-increasing accessibility to health information through new technologies, it is imperative that physicians encourage patients to be knowledgeable consumers beginning at a young age.

Barriers to Effective Communication With Children

The manner in which adults speak to children is influenced by what they think children can understand. Physicians tend to overestimate the understanding capabilities of younger children and underestimate those of older children. Lack of appreciation for the cognitive sophistication of children may result in frustration for all involved. Younger children are presented with information they may not be able to comprehend, and older children may feel frustrated because they are being spoken to as though they are much younger.

Overestimating children's receptivity to medical information can be particularly problematic in the case of children with chronic illness. It is easy to assume that children with chronic medical conditions or those with more hospitalizations would have more sophisticated understanding of illness causation. Although these children may seem more savvy and knowledgeable about medical procedures, little research exists to support the assumption that they have more sophisticated understanding of illness causation than would be expected based on their age or developmental level, or that they are better able than their peers without chronic medical concerns to understand and retain medical information.

Another potential barrier in communicating with children is limiting their participation. Physicians tend to elicit information from children but exclude them from diagnostic and management information. Especially when dealing with chronic or serious illness, children should be asked about their desired level of involvement. Children want to know about their illness and will use whatever information is available to them to make sense of their situation. Developmentally sensitive communication allows children access to usable information, improves their understanding of their situation, decreases fear, and contributes positively to their ability to participate in management.

Providing pediatric care can be both rewarding and enjoyable, but many physicians have been frustrated or pushed to the limit at some point when working with children. On the part of the child, crying or lack of cooperation generally stems from fear or a sense of lack of control over the situation. On the part of the physician, engaging in power struggles or making threatening remarks (eg, "If you're not good, I'll have to give you a shot.") or comparisons between siblings (eg, "Your brother is younger than you and he didn't cry.") are not only ineffective but may make the situation worse. A clear perspective, mindful consideration of developmental level, empathy, and a sense of humor are much more useful.

CASE RESOLUTION

You learn from the mother that her daughter has been in good health. The mother has brought in the child for a routine health maintenance visit. You assess that the child's development is normal and her immunizations are up-to-date. As you and the mother talk, the child appears more relaxed and less frightened. You use the book to engage and distract the child during the examination. She begins to respond to your questions and cooperate with the examination, but she chooses to remain on her mother's lap. Praising a child who is cooperative helps reinforce preferred behavior.

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CHAPTER 4

Talking With Adolescents

Monica Sifuentes, MD

CASE STUDY

This is a first-time visit for a 15-year-old girl who is accompanied by her mother. The mother is concerned because her daughter's grades have been dropping since beginning high school, and she appears fatigued and irritable. The mother reports no new activities or recent changes in the home situation and no new stressors in the family. Both parents are employed, the girl has most of the same friends she has always had, and her siblings currently are doing well academically. The girl is healthy and has never been hospitalized. After the mother leaves the room, the girl is interviewed alone.

Questions

1. When interviewing adolescents, what is the significance of identifying their stage of development?
2. What are important areas to cover in the adolescent interview?
3. What issues of confidentiality and competence need to be discussed with adolescents before conducting the interview?
4. When should information be disclosed to others, despite issues of confidentiality?

Adolescence is a time of unique change from a cognitive, physical, and neurobiological standpoint. Unlike other periods in life in which individuals have at least some knowledge or experience to guide them, adolescence can be characterized by feelings of physical awkwardness, emotional turmoil, and social isolation. In addition, the teenage years are dreaded by most parents, who often feel ill-equipped to handle the unpredictability of their children's responses to puberty and daily social interactions. Rather than directly approach their adolescent, some parents choose to engage in quiet observation. They fully intend to support their children but wait to be approached. Thus, many adolescents do not have the active guidance or timely advice of parents during the teenage years and prefer to spend their time alone or in the company of friends or acquaintances. Fortunately, most adolescents pass through this period uneventfully. In fact, many individuals go through this period gladly and appreciate finally being permitted to drive a car, gain employment, or start dating.

The physician should approach interviews with adolescents differently from interviews with younger children, because with adolescents information comes directly from the teenager rather than a parent (Box 4.1). Unlike an interview with a younger pediatric patient, the adolescent interview should focus on several psychosocial issues that may be uncomfortable to discuss in the presence of a parent. Thus, each teenager should be interviewed alone. The goal of the interview is to help adolescents become more comfortable discussing issues related to physical and mental health with the physician, give adolescents the opportunity to become more responsible for their health care, and discover any psychosocial issues that might interfere with a relatively smooth passage through adolescence.

Box 4.1. Keys to Successful Interviews With Adolescents

- Listen attentively, with minimal interruptions.
- Respect privacy.
- Explain confidentiality.
- Use open-ended, nonjudgmental questions; start with general observations of concern and follow up with specific questions.
- Define medical terms clearly.
- Invite the adolescent to ask questions.
- Help empower the teenager to address health issues.
- Reinforce the teenager's own positive support systems.

Adapted with permission from Sacks D, Westwood M. An approach to interviewing adolescents. *Paediatr Child Health.* 2003;8(9):554–556.

Stages of Adolescence

Adolescents are stereotypically labeled as difficult, complex, and time-consuming patients with complicated concerns that result in nonmedical diagnoses. In addition, they can be accompanied by overbearing, demanding parents, or sometimes no parent.

The quality and quantity of information obtained from the adolescent during the medical and psychosocial interview can be greatly enhanced by taking developmental milestones into consideration. Adolescence can be divided into 3 developmental stages: early, middle, and late (Table 4.1). For example, interest in discussing long-term educational goals varies depending on the age of the adolescent. Most 18-year-olds are prepared to discuss college plans, specific vocational interests, and employment opportunities. In

Table 4.1. Developmental Milestones During Adolescence

Early Adolescence (11–13 years)	*Middle Adolescence (14–16 years)*	*Late Adolescence (17–21 years)*
Concrete, egocentric thought processes	± Abstract thought processes emerge	Abstract thought processes well formed
Parental supervision prominent	± Parental supervision	Limited or no parental supervision
± Risk-taking behavior with feelings of invulnerability	± Risk-taking behavior	Risk-taking behavior diminishes; vocational objectives formalized
± Peer pressure	Peer pressure prominent	Impact of peer pressure decreasing

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contrast, 12-year-olds are still anchored in the concreteness of early adolescence and often are ill-prepared to discuss detailed plans for higher education. Current middle school experiences are much more important to this age group and therefore should be the focus of discussion. Peer pressure is most prominent during middle adolescence; thus, 16-year-olds with friends who smoke cigarettes and drink alcohol likely have tried or use the same illicit substances.

Knowledge of these developmental differences allows the interviewer to more effectively explain instructions and diagnoses to teenagers. For example, compared with 14-year-olds, 19-year-olds can better understand the effects of untreated or recurrent chlamydial cervicitis on long-term fertility. This is not to say that physicians should not discuss these possible consequences with a sexually active 14-year-old with chlamydia; rather, they should use more concrete descriptive wording and repeat the information at future visits. Age guidelines are not rigid, however, and each interview should be individualized to the particular adolescent and the circumstances surrounding the visit.

Issues of Confidentiality and Competence

A discussion about confidentiality is essential and can be approached in 1 of 2 ways. Each method has distinct advantages and disadvantages. To allow conversation to flow more naturally, interviewers should use the approach with which they themselves are most comfortable.

The first approach involves informing adolescents at the beginning of the interview that most issues discussed are held in strict confidence and will not be repeated to anyone. Exceptions are suicidal or homicidal behavior and a history of or ongoing sexual or physical abuse. In any of these instances, other professionals are told of the disclosed information, and parents or guardians ultimately are informed of the disclosure. The advantages of this approach are that discussion of such logistics at the beginning of the interview is less awkward, and the ground rules are clear from the start. This contributes to an atmosphere of trust and honesty. The disadvantage is possible inhibition by adolescents who are unsure about disclosing particular incidents (eg, those concerning sexual abuse) for fear of involving other professionals or family members. Interviewers should be nonjudgmental, reassuring, and empathetic to reduce the possibility of such an occurrence.

The second, less popular approach to the discussion of confidentiality involves informing adolescents at the end of the interview or when and if an exception to maintaining confidentiality arises. Proponents of this approach argue that adolescents tend to respond more honestly to questions when they do not believe physicians will inform others, including their parents or legal guardians. As mandated reporters, however, physicians have a legal responsibility to report sexual and physical abuse; in cases of suicidal or homicidal behavior, it is in the patient's best interest to inform other professionals of this disclosure. The disadvantage to this method is that these issues often arise at very emotional times during the interview, and it is difficult to interrupt the patient to discuss mandated reporting. If physicians wait until the end of the interview to inform adolescents about mandated reporting, however, patients may leave the office feeling deceived and may not return for future visits. For this reason, most health professionals prefer to inform adolescents at the onset of the interview about confidentiality with the hope that it contributes to the development of a trusting relationship.

An assessment of the adolescent's ability to make health-related decisions is another important aspect of the interview. *Competence* is the ability both to understand the significance of information and to assess alternatives and consequences to sufficiently identify a preference. Various factors other than age must be considered, such as maturity level, intelligence, degree of independence, and presence of any chronic illness. This last factor is included because adolescents with chronic conditions may have already participated in decisions about their health care. Regardless, it can be difficult to assess competence from just 1 visit. It may not even be necessary to make an assessment emergently, except in certain cases, such as with an unplanned pregnancy.

Although it is imperative to interview adolescents alone, every attempt should be made to involve parents or guardians in physical and mental health decisions. Although specific state laws allow physicians to treat minors in emergent situations and in cases of suspected sexually transmitted infections without the consent of a parent or guardian, physicians should urge adolescents to inform their parents or guardians of any ongoing problems disclosed during the interview. The ultimate decision, however, rests with the adolescent. Physicians can assist adolescents in discussing delicate issues with their parents by role-playing with teenagers or by sitting in on the conversation between the adolescents and their parents when disclosing sensitive information. Health professionals should become familiar with the specific consent laws related to minors in the state in which they practice medicine to confirm the legal abilities of minors to consent to sensitive health care services.

Psychosocial Review of Systems

A major part of the adolescent interview involves obtaining a thorough psychosocial history, which typically can be completed in 20 to 30 minutes. The approach, which is known by the acronym *HEADSS* (home, employment and education, activities, drugs, sexuality, suicide/depression), allows interviewers to evaluate the critical areas in adolescents' lives that may contribute to a less than optimal environment for normal growth and development (Box 4.2). Questions about sexuality, sexual orientation, and gender identity must be asked in a nondirected, open-ended, nonjudgmental fashion, giving adolescents time to respond. This information is imperative to adequately assess risks for conditions such as social isolation, unintended pregnancy, and sexually transmitted infections, including HIV. In addition, an inquiry about sexual, physical, and emotional/verbal abuse is indicated during this part of the interview.

Because most adolescents now have access to the internet 24/7 via their cell phone, home computer, or other electronic device, it is important to discuss screen time with them and their parents to obtain a more accurate picture of their online activities, connectedness with peers and family, and sleep hygiene practices. In addition to reviewing the amount of time spent on an electronic device each day, physicians also should inquire about texting, sexting, and whether the patient is a victim or perpetrator of cyberbullying.

Issues That Need Immediate Attention

Many issues discussed during the psychosocial interview can be a source of significant stress and anxiety for adolescents. Evidence of psychological or adaptive difficulties must be taken seriously and should be reassessed at future visits. Certain disclosures, however, demand immediate attention. Suicidal ideation, with or without a previous attempt, requires a more in-depth analysis of the gravity of the problem. Mental health professionals should be involved emergently in the clinical assessment of these precarious situations. Other issues that require immediate attention include possible danger to others and a history of or ongoing sexual or physical abuse. Depending on the specific circumstance, issues such as a possible or confirmed unplanned pregnancy, bullying, substance use, and sexual orientation may not necessarily require the emergent

Box 4.2. What to Ask

HEADSS

H: Home

- With whom does the adolescent live?
- Have there been any recent changes in the living situation?
- How are things between parents/other adults living in the home?
- Are the parents or guardians employed?
- How does the adolescent get along with the parents and siblings?
- Does the adolescent feel safe at home? In the neighborhood?
- Is there a firearm in the adolescent's home? If so, what does the adolescent know about firearm safety?

E: Employment and education

- Is the adolescent currently in school?
- What does the adolescent enjoy about school? Dislike?
- How is the adolescent performing academically?
- Has the adolescent ever been truant or expelled from school?
- Are the adolescent's friends attending school?
- Is the adolescent currently employed? How many hours does the adolescent work each week?
- What are the adolescent's future education/employment/vocational goals?

A: Activities

- What does the adolescent do in his or her spare time?
- How much time is spent on technology (the computer, cell phone, other electronic devices) during the day and at night?
- What does the adolescent do for fun? Is the adolescent ever bored?
- With whom does the adolescent spend most of his or her time?

D: Drugs

- Do any of the adolescent's friends smoke tobacco, use electronic cigarettes, vape, or use illicit drugs or alcohol?
- Is the adolescent currently using, or has he or she ever used, tobacco, electronic cigarettes, or vaporizer?
- Is the adolescent currently using, or has he or she ever used, any illicit drugs? What about steroids? Alcohol?
- Does the adolescent ever feel pressured by friends to use drugs or alcohol?

S: Sexuality

- What is the adolescent's sexual orientation and/or gender identity or expression?
- Is the adolescent currently in a relationship?
- Is the adolescent sexually active?
- If so, what was the age of the adolescent's first sexual experience?
- What types of sexual experiences has he or she had?
- How many sexual partners has the adolescent had in his or her lifetime?
- Does the adolescent have a history of sexually transmitted infections?
- Does the adolescent (or the partner) use condoms or another method of protection?
- Does the adolescent (or the partner) use any methods of contraception?
- Does the adolescent have a history of sexual or physical abuse?

S: Suicide/depression

- Is the adolescent bored all the time? Ever sad or tearful? Tired and unmotivated?
- Has the adolescent ever felt that life is not worth living or ever thought of or tried to hurt their self? More importantly, does the adolescent have a suicide plan or access to a firearm?

Adapted with permission from Goldenring JM, Rosen DS. Getting into adolescent heads: an essential update. *Contemporary Pediatrics.* 2004;21:64.

involvement of other providers initially; however, close follow up must be assured and arranged by the physician or other health professional regardless of consent by a parent or guardian.

Concluding the Interview

The adolescent interview should be conducted at a time when the adolescent is relatively healthy and the interviewer has set aside ample time for a thorough, uninterrupted discussion. However, all topics need not be addressed during the initial interview if time does not permit and the adolescent appears relatively stable based on initial screening. Issues that are not covered in depth at this visit can be addressed at the next one. The number of appointments needed to discuss or work through a particular problem or concern is unlimited.

At the end of each visit, the interview should be summarized, any difficult topics identified, and the issue of confidentiality reviewed once again. Adolescents should then be asked to identify a person whom they can trust or confide in should any problems arise before the next visit. In some instances, this issue may already have been discussed during the interview. Adolescents also should be given the opportunity to express any other concerns that were not addressed in the interview and ask additional questions.

The physician should clearly point out to the adolescent any significant risk factors or risk-taking behaviors that have been identified during the interview and assess the teenager's readiness to change this behavior. For those adolescents who are not engaging in high-risk behaviors, the physician should acknowledge that things seem to be going well, praise them with sincere positive feedback, and review their individual strengths and accomplishments. Available resources, such as teen hotlines and popular websites, should be given to the adolescent prior to inviting the parent or guardian back into the examination room. General concerns should then be reviewed with the parent or guardian while maintaining the adolescent's confidentiality. The parent or guardian also should be given appropriate written or electronic resources to review, particularly if a sensitive subject has been discussed, and invited to call the physician if any additional questions or concerns arise. The follow-up appointment should be arranged with the adolescent before the conclusion of the visit.

CASE RESOLUTION

The adolescent should be informed about confidentiality and the specific exceptions to maintaining it. Nonthreatening topics, such as home life, school, employment, and other outside activities should be explored first, followed by questions about sexuality, gender, sexual orientation, sexual activity, and illicit drug use. Suicidal behavior or depression and safety issues should also be reviewed with the teenager alone and again with the parent if there is a need for a more formal or immediate mental health evaluation. In addition, computer and cell phone use as well as sleep hygiene should be evaluated. Identified high-risk behaviors and their consequences should be discussed with the adolescent at the end of the interview, and a plan for future visits should be arranged. The mother should then be invited back into the examination room prior to the conclusion of the visit to discuss nonsensitive issues unless permission has been obtained from the teenager to disclose and discuss confidential topics.

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CHAPTER 5

Telephone Management and E-medicine

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CASE STUDY

The mother of an otherwise healthy 10-month-old girl calls and tells you that her daughter has a fever. The girl's rectal temperature has been 39.4°C to 40.0°C (103°F to 104°F) for the past 2 days. Although she is fussy with the fever, she plays normally after receiving acetaminophen. The girl is eating well and has no runny nose, cough, vomiting, diarrhea, or rash.

Mother also mentions 2 other concerns that she has been meaning to bring up with you. The first involves questions about feeding and how to introduce table foods; the other is sleep problems. Her daughter has been waking up several times a night for the past month, and mother feels exhausted.

Questions

1. How do telephone and face-to-face encounters between physicians and patients differ?
2. What are some general guidelines for effective doctor-patient communication via telephone?
3. What historical information is necessary for appropriate telephone management?
4. What points are important to cover in home treatment advice?
5. For nonurgent issues, what are the possible roles of telephone encounters or e-medicine in patient care?

Parents and guardians are increasingly accessing their children's health professional through avenues other than a typical office visit. Telephone management and electronic communications make up a substantial portion of a primary care physician's time. It is estimated that pediatricians spend more than 25% of their total practice time engaged in telephone medicine. Telephone management includes triage of acute illness symptoms as well as ongoing preventive care and management of chronic conditions. Electronic communication also plays an increasing role in acute, chronic, and preventive care.

Telephone Management for Acute Illness

The main components of a telephone management encounter for acute illness mirror those of an office visit: establish rapport, gather a complete history, formulate an assessment and plan, ensure adequate follow-up, and document the encounter. The key difference is that often a telephone call offers no opportunity for a physical examination or direct observation of the child; however, video conferencing and the ability to send photographs electronically is beginning to minimize this difference. Obtaining a thorough history remains the critical component of telephone management, however. Closed-loop communication, with the parent/guardian or patient repeating back to the physician the plan of care, is also an important component of the telephone consultation.

Telephone Communication Skills: Establishing Rapport

Parents and guardians commonly call their pediatric health professional because they are worried about their child. The friendly voice of a staff member in the health professional's office has a substantial role in reassuring an anxious parent. Each call should begin with a "verbal handshake." Staff should identify themselves and the place in which the call is received and offer to help. They should learn the caller's name, the caller's relationship to the child, and the child's name. Using the child's name in conversation helps establish rapport and creates a more personal atmosphere.

Telephone calls for medical advice are often received in busy environments, such as emergency departments (EDs) or clinics, in which other patients are waiting to be seen. It is easy to be abrupt under these circumstances and not give complete attention to a caller. If a call is not an emergency, staff members can take the caller's telephone number and return the call as soon as possible. The health professional who is returning a call to a patient should ensure it is a good time for the patient to receive a return call. Unsafe

practices, such as talking while driving, should be avoided by both the health professional and the patient.

Studies show that the length of a patient visit does not correlate with patient satisfaction. Telephone encounters need not be lengthy; the average length of a call is reported to be 3 to 5 minutes, depending on the setting. Each call must be pleasant, however, and address the caller's concerns. Open-ended statements and questions, such as, "Tell me about your child's illness," or "Are there any other symptoms?" are useful at the beginning of a call because they give the caller an opportunity to explain the situation without interruption.

Establishing rapport is more difficult on the telephone than in person because on the telephone the health professional is limited to verbal communication. In face-to-face encounters, the health professional can use words as well as means of nonverbal communication, such as facial expressions, eye contact, gesturing, and touch, to convey warmth and empathy. The health professional should use various aspects of verbal communication to convey sincere interest in a caller's concerns and should pay attention to these verbal cues from the caller. Many components of verbal communication, including vocal expression, pace, articulation, tone, volume, and pauses, affect telephone interactions. The health professional should speak clearly and use vocabulary that the caller understands. Medical jargon should be avoided. A friendly yet respectful tone and a calm, professional manner should be maintained.

Careful listening is crucial to obtaining the information necessary to make medical decisions over the telephone. One of the major goals of the health professional is to recognize and respond to the caller's main concerns and expectations. Researchers have found the following questions useful in the identification of parents' chief concerns: "What worries you the most about [use child's name] illness?" and "Why does that worry you?"

In interacting with a caller who rambles, it may be necessary for the health professional to focus the conversation. Asking the question, "What can I do to help?" should clarify the reason for the call. If it is necessary to verify information, the professional can summarize what has been heard and ask if they have understood correctly. Using a triage protocol book or similar resource can help the health professional streamline questions and aid in correct disposition of the patient.

The angry caller may elicit defensive or confrontational behavior from the health professional. Responding to anger with arguments is time-consuming, stressful, and pointless. The health professional should be warm and understanding to create an environment in which a caller who wishes to discuss his or her feelings is comfortable. Acknowledging anger may encourage open discussion and problem-solving (eg, "You sound upset. I am ready to help you. What can I do?"). Empathizing with the caller (eg, "I don't blame you for being upset"; "That must have been very frustrating.") and apologizing if the caller has experienced delays or barriers in accessing care is also helpful.

The health professional can build confidence in the caller by validating the steps that individual has already taken, such as, "You did the right thing by giving your child acetaminophen for the fever. That is exactly what I would have done." "I'm glad that you called about this." The health professional may even be able to offer reassurance to a parent or guardian who is not managing the child's illness correctly by commenting that many parents and guardians try the same treatment. After providing that reassurance, a different treatment approach can be suggested.

Before the end of the conversation, the caller should be asked to "teach back" or summarize what the health professional has recommended and encouraged to call again if additional problems occur. For example, the physician might say, "I want to be sure I explained myself clearly. Can you tell me what you are planning to do now for your child?" Giving clear guidance about reasons to seek emergency care is particularly important.

Telephone History Taking

Most calls for triage of an acute problem are about upper respiratory symptoms, fever, rash, trauma, or gastrointestinal symptoms, that is, the same problems most commonly encountered in the office. With standardized history taking and home care advice, many patients with these chief concerns can be safely managed at home. Several excellent published telephone management protocols can aid the health care team in advising patients efficiently and appropriately. Many practices use nurses as the first point of contact for telephone triage, with the pediatrician serving as second-tier triage for more complex or worrisome concerns.

For the history obtained via telephone, it is necessary to gather sufficient information to make an appropriate decision. Questions should be asked with the aim of determining whether an emergency exists and making a diagnosis. The health professional should follow the same organized approach that would be used in the office setting (Box 5.1). Key features, such as patient age and past medical history, should guide questioning. For example, if the mother of a 20-day-old girl reports that the neonate has a temperature of 38.9°C (102°F), it is necessary to see the newborn in person immediately. An older child with the same chief report of fever may be safely managed at home, however, depending on the answers to other questions about additional symptoms. Similarly, knowledge that a child who has been exposed to chickenpox has a compromised immune system is crucial in providing appropriate telephone advice.

Additional specific questions should be asked to clarify the child's condition and obtain all the information necessary to make a good decision. Many physicians can access electronic medical records (EMRs)

Box 5.1. What to Ask

- How old is the child?
- What is the child's chief problem? What are the child's symptoms?
- How long has the child had these symptoms?
- How is the child acting?
- Does the child have any chronic illnesses?
- Is the child taking any medications?
- What are you most worried about?

remotely to review the child's record, which can greatly aid in obtaining a thorough history. If review of the medical record is possible, it is reassuring for the health professional to share that information with the child's caregiver by stating, for example, "I am reviewing your child's medical record in the computer so that I can be sure I have all the information I need to give you good advice."

The physician should focus on the critical features that will affect disposition of the patient (ie, ED vs office visit vs home care). For example, for the child who is vomiting or has diarrhea, the state of hydration is critical; for the child with a cough, the occurrence of breathing difficulty is critical; and for the child with head trauma, loss of consciousness is critical. Methods of teaching telephone management skills include role-playing, listening to mock parent calls, and reviewing tapes of actual calls.

Telephone Advice: Communicating the Assessment and Management Plan

In an emergency situation, that fact should be explained to the caller and appropriate follow-up plans made, such as advising the parent or guardian to call 911 for life-threatening conditions such as respiratory depression or uncontrollable bleeding. If the condition is potentially serious but non–life-threatening (eg, right lower quadrant pain or possible fracture), the caller should be advised to bring the child by car to the ED or physician's office within a specified amount of time. For other types of calls, the health professional must decide if and when the child should be seen by a physician and the appropriate course of home treatment.

Because most childhood illnesses are mild and self-limited, evaluation of the safety of medical advice obtained by telephone requires large samples to detect poor outcomes associated with mismanagement. Research has described a "wellness bias" in which health professionals, who primarily see patients with mild, self-limited illnesses, may downplay the severity of reported symptoms and choose the most benign diagnostic possibility. This bias may be more pronounced in a telephone encounter, in which the physician cannot see the child. One study reported telephone encounters in which physicians seemed to make a decision early in the conversation and then "shut out" additional information that should have led to the consideration of more serious diagnoses. The safest approach is to always have a high index of suspicion for a serious condition and to ask questions to confirm or dispel those suspicions. Research shows that parents expect to receive an explanation of their child's illness. The health professional should clearly state what the child's illness seems to be, the likely cause, and what the parent or guardian can anticipate (eg, length of time that the child is likely to be sick, additional symptoms that may appear).

Before giving any treatment advice, the health professional should ask the caller the following questions: "What have you done so far?"; "Have you given the child any medications?"; and "How is this treatment working?". If the therapy seems appropriate, the caller should be encouraged to continue the treatment. Alternatively, the regimen should be modified as indicated. Instructions for home treatment should be clear and as easy as possible to implement. If the instructions are complicated or lengthy, the health professional may ask the caller to write them down. When prescribing medication, the physician should ask if the child has any known drug allergies; for the prescribed medication the physician should give the dose, frequency of administration, and information about possible side effects. The health professional should verify that the caller can follow the telephone advice (eg, a parent has a thermometer and knows how to use it).

Closing the Encounter: Ensuring Appropriate Follow-up

The health professional should confirm that the caller understands the information and instructions and agrees with the plan. Asking questions such as, "What questions do you have?" encourages callers to raise uncertainties and ask for needed clarification. Most important, if the decision is to manage at home, the caller should always receive specific instructions about when to call back. The caregiver should call if the child's symptoms change, persist, worsen, or cause anxiety to the parent or guardian. Additionally, symptoms specific to the child's condition should be followed and the caregiver advised on when to call back or come in (eg, fever of >2 days' duration, irritability, decreased urination). If the physician plans to check up on the child by telephone, the physician should confirm and record the appropriate callback number or numbers. The caregiver who seems unduly anxious or uncomfortable with home treatment should be given the opportunity to have the child seen in person by a health professional.

Documentation

All calls for medical advice should be documented in the child's medical record for medical reasons (eg, better follow-up, improved continuity of care) and legal purposes. The form used for documentation should include the date and time of the call; the name, identity, and telephone number of the caller; the name and age of the child; the chief symptom; other symptoms; possible diagnoses; advice given; and the name of the person who took the call.

Privacy and Technology Considerations

Many calls take place over cell phones. The caller may be able to see the telephone number from which the physician is calling. The caller should be given clear instructions as to the appropriate avenue for calling the physician, for example, "Please call back to the nurse triage line if you need to talk to me again." Clinic staff may wish to give their patients access to a "direct line" to call back to the clinic so that patients do not have to go through an automated telephone triage with each return call. Some health professionals may choose to block their numbers so they are not visible by caller identification. Others may feel comfortable having a parent call directly to their cell phone but should give clear guidelines about doing so.

Many cell phones have the capacity for taking and sending photographs. A photograph can be a valuable additional piece of information when evaluating symptoms, such as rash. However, it is important for the physician to educate or remind the caller that data sent by cell phone is not secure. Many EMRs now include the option for patients to upload their own photographs or for health professionals to use a secure application to capture photographs for documentation in the medical record. The latter method is preferred.

Telephone Management: Preventive Care and Care Coordination

Telephone encounters can provide an excellent opportunity for preventive care and anticipatory guidance. Issues such as sleep problems or behavioral issues may be difficult to discuss during an office visit with the child present. Telephone follow-up provides an opportunity to minimize distraction during conversation between parent or guardian and physician. Some pediatric offices develop protocols and charge a fee for prolonged telephone consultation.

Telephone follow-up can also help facilitate care coordination for children with chronic health conditions. For example, a physician who recommends medication changes for a child who presents with poorly controlled asthma can have a follow-up call with the parents 1 month later to assess asthma symptoms. Using telephone follow-up when appropriate allows the health professional to provide patient-centered care (ie, individualize care to the patient's needs) and minimize missed work and school for patients and families.

E-medicine

Virtual medicine, or e-medicine, is an increasing avenue for communicating with patients. Studies suggest that up to 75% of patients would like to communicate with their physician through email. Patients and parents who choose electronic communication as a means of interacting with their physician report high rates of satisfaction and tend to have higher levels of education.

Email communication can be convenient for patients and families and may increase patient-centered care. Specific American Academy of Pediatrics, American Medical Association, and American Medical Informatics Association guidelines exist for the use of email with patients. Traditional email poses a variety of data security concerns, however. Therefore, many EMRs incorporate the ability for patients and their parents or guardians to interact directly with the EMR. This includes the ability to view laboratory test results, immunization records, growth charts, and patient problem lists. Additionally, it may be possible for a parent or guardian to send a secure message with a health question to the health care team. Clinic staff should create guidelines for patients and parents or guardians about appropriate issues to be addressed through electronic messaging, expected response time, and who will provide a response (ie, nurse or physician).

Communication through the EMR should be professional, concise, and to the point. Written communication has the benefit of eliminating sequential missed calls back and forth (ie, "telephone tag") when attempting to reach a parent or guardian by telephone. The physician should remember, however, that written communication is interpreted through the lens of the reader. Delicate or complex conversations should first be broached by telephone or in person. Similar guiding principles apply with telephone and email communications; the physician must establish rapport, give clear advice, and provide guidance for follow-up. Attention should be paid to correct grammar and spelling in emails, because errors may decrease confidence in the physician. Electronic communication can also be a useful method to provide patient education materials, such as a link to a helpful website.

Physicians should work with their health care system to clarify types of communication that are best transmitted electronically. For example, straightforward questions may be answered with a simple email message, but more complex care needs may be appropriate for a formal e-visit that can be billed to insurance. Research suggests that insurance plans may influence how patients choose to use e-medicine. For example, the patient with a high deductible insurance plan may prefer to first contact the health professional through an e-visit to determine if an in-person office visit is necessary.

Health Care Disparities

When developing telephone and e-medicine options, it is necessary to pay particular attention to meeting the needs of patients with limited English proficiency. Studies have shown that patients with limited English proficiency use e-medicine less frequently than patients with English proficiency, particularly for tasks such as requesting medication refills. Additionally, 1 study showed that in telephone encounters, patients with limited English proficiency disagreed with the care recommendation and tended to receive advice to seek higher acuity care more often than patients with English proficiency. Recommendations to promote health equity include continuing to explore ways to ensure that telephone and e-medicine are being delivered in a manner that is equitable and patient-centered for all patients.

Conclusions

Telephone management and e-medicine represent the changing face of medical practice. The health professional should be prepared to deliver care that meets the needs of the patient, which may necessitate being creative with how and where care is delivered. The approach must be tailored to each patient scenario, and physicians should continually strive to adapt their approach so that they can provide effective and appropriate patient-centered care both in and out of the office.

CASE RESOLUTION

The physician learns several facts that result in the recommendation that the child be seen that day. (Had the call been received at night, a visit the next day would have been advised.) These facts include the child's age, the height and duration of the fever, and lack of any symptoms of localized infection.

The other concerns of feeding questions and sleep issues present excellent opportunities for management through a follow-up telephone call, electronic communication, or office visit, depending on parent preference and clinic resources.

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CHAPTER 6

Informatics

Alan Tomines, MD

CASE STUDY

You are a physician in a small pediatric practice. Your hospital implemented an electronic health record system, which has been made available within the hospital and in the offices of its affiliated practices. The hospital chief of staff asks you to participate on the hospital's informatics committee. You have served in the past on other clinically oriented steering committees, but you do not consider yourself a technology expert and you express your trepidation to the chief of staff, who asks you to speak with the head of the informatics committee.

Questions

1. What are the important informatics concepts to understand?
2. What are the important drivers of health information technology?
3. What are the challenges to physician acceptance of electronic health records?
4. What are the special pediatric considerations in electronic health records?

To make optimum clinical decisions, physicians must have information about their patients' health that is current, accurate, reliable, and complete. The physician should be able to access this information wherever and whenever necessary. To the extent possible, the physician should be presented with information that fosters an evidence-based approach to decision making, and the decisions made should be communicated to other health professionals in a manner that is clear and error-free. The physician should be able to review measures of the quality of care provided. Health information technology (HIT) holds the promise of increased access to patient health information, improved patient safety, reporting of desired health outcomes, and improved health care efficiency with the potential for decreased health care expenditures. The implementation and acceptance of HIT is not without challenges, however.

Basic Concepts

Although the terms "data," "information," and "knowledge" are sometimes used interchangeably, these are distinct concepts. *Data* are mere observations or facts (eg, hemoglobin equal to 9 g/dL). *Information* is data placed in meaningful context (eg, hemoglobin equal to 9 g/dL in a 3-month-old who is breastfed). *Knowledge* is the understanding of information, including an assessment of its completeness (eg, hemoglobin equal to 9 g/dL in a 3-month-old infant who is breastfed may represent a physiologic nadir but may also represent blood loss, increased destruction of red blood cells, or decreased production of red blood cells).

Information technology refers to any hardware or software that supports the management of data, including how the data are acquired, stored, retrieved, transformed, interpreted, and disseminated. For example, a *database* is an organized collection of data that facilitates the storage and retrieval of those data. An *information system* is the sum of the people, work processes, and information technology that supports an activity. Depending on the degree to which technology is applied, the processes of an information system may be automated, manual, or a combination of both.

Informatics Defined

Medical informatics is the science of the appropriate application of information technology to health care work processes. Specialists in informatics (referred to as *informaticians* or *informaticists*) serve as liaisons between clinical and technology staff to ensure that HIT is optimally applied to address clinical information and workflow needs. Medical informatics places great emphasis on nontechnologic considerations that can affect the successful implementation and acceptance of health information systems, including information science, cognitive psychology, project management, organizational and change management, health care policy, and ethics.

The field of medical informatics can itself be subdivided into specific clinical domains, such as nursing, pharmacy, veterinary medicine, dentistry, and imaging. *Biomedical informatics* is a term of broader scope that encompasses medical informatics; bioinformatics, in which the primary domain is genomics and bioengineering; and public health informatics.

Electronic Health Information Systems

All electronic health information systems ultimately are used in managing some aspect of patient care, and for ease of discussion in this chapter these systems are presented in 4 broad categories: electronic records of patient care, ancillary clinical systems, administrative systems, and telemedicine. Table 6.1 lists several common abbreviations used in electronic health information systems and informatics.

Table 6.1. Abbreviations Used in Informatics

Abbreviation	*Expansion*
ARRA	American Recovery and Reinvestment Act of 2009
CDR	Clinical data repository
CDSS	Clinical decision support system
CPOE	Computerized physician order entry
EHR	Electronic health record
EMR	Electronic medical record
eRx	Electronic prescribing
HIE	Health information exchange
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIS	Hospital information system
HIT	Health information technology
HITECH	Health Information Technology for Economic and Clinical Health Act
IIS	Immunization information system (also known as an immunization information registry)
LIS	Laboratory information system
P4P	Pay for performance
PACS	Picture archiving and communication system
PHI	Protected health information
PHR	Personal health record
RIS	Radiology information system

Electronic Records of Patient Care

A *medical record* serves as the legal record of care provided to a patient by a health professional or health care organization. An *electronic medical record* (EMR) is an information technology that supports the traditional role of the medical record, including serving as an archive for clinical documentation, such as physician orders, progress notes, and laboratory and imaging results. A full-fledged EMR is more than an electronic version of the traditional paper-based record, however. It provides capabilities that support the enhanced delivery of care.

Important components of an EMR include a clinical data repository, a clinical decision support system, and computerized physician order entry. A *clinical data repository* (CDR) is a real-time database containing the clinically relevant patient data of an institution. It supports timely access of patient information for physician decision making and provides information used by other EMR components. A *clinical decision support system* (CDSS) is a special computer program that applies medical knowledge to data from a CDR to produce patient-specific care recommendations. A *computerized physician order entry* (CPOE) is a specialized computer program that allows health professionals to write electronic orders that are directed to the appropriate clinical staff or ancillary department. A CPOE can decrease errors resulting from illegible handwriting, decrease delays in the receipt and execution of orders, and allow entry of orders away from the care setting. Additionally, a CPOE paired with a CDSS can leverage patient-specific information in a CDR to prevent harm resulting from drug-drug interactions, drug-allergy interactions, or errors in age- or weight-based dosing.

Although an EMR generally operates within the functional boundary of a hospital or practice, the history of a patient's health care is not limited to these settings. The *personal health record* (PHR) is a summary of an individual's health history—usually self-maintained—that contains information collected from encounters with different health professionals, medicolegal documents (eg, living wills, advance directives), and other health information that may be relevant to patients (eg, regimens for nontraditional remedies, logs of home testing for blood pressure or glucose). The concept of a PHR is not new; patients with multiple medical problems have long maintained paper-based PHRs out of necessity to ensure they have at least 1 reliable and portable source containing a complete medical history. The electronic PHR is an evolving entity, ranging from scanned paper documents stored on portable devices to web-based applications that connect with EMRs and capture data from medical devices. The PHR is not considered a legal record of care.

The next stage in the evolution of the EMR is the *electronic health record* (EHR), which has the functionality of a full-fledged EMR with the additional capability for exchanging data among multiple different EMRs to provide the entire longitudinal history of the patient. With this data exchange capability, an EHR may also support the needs of population health, such as identification of patient-applicable clinical trials, mandatory reporting of notifiable disease, and provision of anonymized clinical data to support clinical and public health research. (The term EHR has been used interchangeably with and has largely supplanted the term EMR.)

A *health information exchange* (HIE) is an enabling technology that acts as a hub for the secure exchange of data between EHRs. Via an *interface* (a program that allows 1 information system to communicate with another), an EHR can connect to an HIE and exchange health information with other EHRs that are connected to that HIE. Although an HIE generally serves a specific geographic region, in future the interconnection of HIEs may allow an EHR in 1 region to share data with an EHR in another region, thereby providing nationwide or worldwide access to a patient's entire history of episodic care.

Ancillary Clinical Systems

Ancillary clinical systems provide information management and automation for specific health care services or domains, including pharmacy, laboratory, imaging, and immunizations.

A *pharmacy information system* tracks patients' prescription and payment information and can improve patient safety by checking for medication interactions and appropriate dosing. A related concept is *electronic prescribing* (*e-prescribing* or *eRx*), which is a specialized type of CPOE that allows physicians to prepare and transmit prescriptions electronically to a pharmacy information system.

When connected to an EHR, a pharmacy information system can receive and process prescriptions, and send back dispensing information to support medication reconciliation.

Laboratory information systems (LISs) are used to manage the receipt of laboratory orders, track specimens, capture data from automated analyzers, and present laboratory results to the ordering health professional via direct access to the LIS, or via an interface that transfers the results to an EHR. An LIS can support patient safety through timelier access to laboratory results and data for use in making individualized patient care decisions.

A *picture archiving and communication system* manages the storage and distribution of patients' electronic medical images, which often are captured directly from computerized or digital radiography devices, as well as other imaging modalities (eg, computed tomography, magnetic resonance imaging, ultrasonography). A *radiology information system* incorporates the functionality of a picture archiving and communication system while managing other service activities, such as reporting, scheduling, and billing.

An *immunization information system* (IIS, also referred to as an *immunization registry*) is used to document and track patient vaccinations. An IIS can send reminder or recall notices, as appropriate, to physicians and parents or guardians when vaccinations are due or when administered vaccines are determined to be ineffective or unsafe. An IIS usually is maintained regionally by public health entities; thus, it also collects reports on adverse vaccine events and provides summaries of regional vaccination prevalence. These systems usually have the capability to exchange data with capable EHRs.

Administrative Systems

A *hospital information system* comprises all the clinical and nonclinical information systems of an institution. A hospital information system may be a single integrated information system or may represent multiple interconnected information systems. Hospitals and large practices often have separate information systems to manage individual administrative functions, such as appointment scheduling, insurance eligibility, and billing and payment. A *practice management system* is an information system designed to manage administrative tasks for small- and medium-sized clinical practices.

Telemedicine

Telemedicine is not an information system per se but a related concept of interest in informatics. *Telemedicine* is the use of information and communication technologies to deliver health care over a distance, often to support patient care in rural or underserved areas. Many specialties exist within telemedicine, and they roughly correspond to distinct medical specialties, such as *teleradiology* (ie, the transmission of radiologic images electronically for interpretation) and *telesurgery* (ie, the use of video and robotic technology to perform surgery). The use of email and websites to consult with patients is also a form of telemedicine.

Key Drivers for Adoption of Informatics

The key drivers for the adoption of HIT are improved patient safety, the ability to measure health care outcomes, increased efficiency of work flow in the patient care setting, and reduced health care expenditures.

Improved patient safety through the reduction of preventable errors is the primary driver of information technology adoption in many health care organizations. In the report *To Err Is Human: Building a Safer Health System,* the Institute of Medicine (now known as the Health and Medicine division of the National Academies) estimated that up to 98,000 deaths annually in the United States are attributable to medical errors. Most errors were noted to be preventable and caused by systems and processes that increase or fail to prevent human errors. Computerized physician order entry is an EHR technology with the potential to improve patient safety by alerting a physician to errors before an order is submitted in an EHR.

Changes in the health care marketplace are driving the measurement of health care outcomes. *Pay for performance*, which relates payment to measures of quality of care provided; medical "report cards" that permit comparison of health care plans and professionals; and accountable care organizations are examples of market drivers. Electronic health records are critical to collecting and analyzing data to calculate these measures. Additionally, the decision support system of an EHR may improve health care outcomes through guideline adherence, such as by reminding both physicians and patients about care options that may have been overlooked.

Improvements in efficiency are another driver in the adoption of information technology. For example, efficiency can be gained by automating highly repetitive, data-intensive activities such as billing and scheduling. The introduction of information technology into a clinical setting without thorough consideration of effects on work flow, however, may introduce unanticipated workflow consequences that decrease efficiency or result in the creation of workarounds that reduce the effectiveness of the newly implemented technology.

In 2016, health care spending represented nearly 18% of the gross domestic product of the United States and increased at a rate nearly twice that of inflation. Information technology is considered to be a possible source of cost savings because its use has the potential to reduce duplication of diagnostic studies as well as the time spent on administrative tasks. As predicted in the 2001 report *Crossing the Quality Chasm: A New Health System for the 21st Century,* the use of email has served to meet the needs of patients more quickly and at lower cost than a traditional visit.

Challenges

Despite the existence of significant health care drivers for the adoption of informatics, several challenges prevent the easy implementation and acceptance of HIT, including information security, technology costs, organizational change, system usability, and the effect on physician-patient interaction.

The ease with which information systems can exchange data should not belie the care required to protect electronic patient data. *Protected health information* (PHI) is any information about a patient (eg, name, medical record number) that may be used to identify that patient. Patients have the expectation that their PHI will be kept private; health professionals' assurance that private information will not be revealed is referred to as *confidentiality*; the policies and technologies that support confidentiality are called *security*. The Health Insurance Portability and Accountability Act of 1996 defines the measures that must be taken to ensure that PHI is kept secure and is made available only to authorized individuals or organizations participating in a patient's health care. Although health information systems often use sophisticated technical barriers to protect patient data, recent instances have occurred in which hospitals' EHRs have been accessed and control of them gained by unauthorized parties who sought ransoms to restore control of the EHR. Generally, such data breaches are the result of failure to adhere to security safeguards, such as sharing passwords or failing to update security software. Educating health professionals is critical to ensuring the confidentiality of patient data.

The cost of implementing health information systems can be prohibitive for health care delivery organizations, particularly small practices. To address this barrier, the Health Information Technology for Economic and Clinical Health (HITECH) Act was included in the American Recovery and Reinvestment Act of 2009. The HITECH Act authorized the provision of Medicare and Medicaid incentives to physicians and hospitals that adopt EHRs and demonstrate "meaningful use" of EHRs by meeting specific objectives toward improved health care delivery and outcomes. These objectives include using EHRs for basic activities, such as recording patient demographics and vital signs; maintaining active problem, medication, and allergy lists; providing patients with summaries of outpatient visits and inpatient discharge instructions; electronic prescriptions and CPOE; and providing drug-drug and drug-allergy checks. The objectives also include more complex functions, such as providing data to public health agencies for disease surveillance as well as immunization and cancer registries; generating lists of patients with specific conditions for quality improvement and research; identifying and providing patient-specific education resources; and supporting medication reconciliation and care summaries across health care settings. To assure physicians and hospitals that they are adopting EHRs that allow them to meet meaningful use regulations, the US Department of Health and Human Services developed criteria for certifying EHRs. By 2016, more than 95% of eligible hospitals and 60% of office-based physicians had demonstrated meaningful use of certified EHRs.

Management of organizational change is an important part of successful information system implementations. Introduction of technology inevitably results in workflow changes for physicians and nurses and may result in repurposing of administrative staff. Resistance to these changes should be anticipated, and strategies to mitigate resistance should be instituted, including involvement of health professionals in the selection and ongoing enhancement or optimization of EHRs.

It is also important to consider the effect of technology on the patient-physician interaction. Physicians increasingly engage in electronic documentation and ordering during patient visits. Although some patients have a favorable opinion on the use of HIT, physicians should be sensitive to patients who feel that technology is intrusive; as appropriate, physicians should acknowledge the intrusion and identify potential benefits to the patient, including efficiency of access to information and more efficient communication of prescriptions to pharmacies or orders to ancillary services. Additionally, physicians should remain vigilant and not allow the EHR to detract attention from their patients during the office visit.

Human-computer interaction is the study of the interactions between people and information technology. It is important for users to perceive that the technology is both useful (ie, supports the work being done) and usable (ie, readily learned, efficient, helps in avoiding and correcting errors). Perception by the physician that an EHR is difficult to use or interferes with patient care or patient interaction may impede the acceptance of EHRs as supportive tools. The topic of usability of HIT is an emerging area of research in the field of informatics.

Pediatric Considerations

Although certified EHRs are present in more than 95% of hospitals, only 3 in 4 children's hospitals have successfully demonstrated their meaningful use; similarly, pediatricians trail other primary care specialists in demonstrating the meaningful use of EHRs. Although pediatric patients represent approximately 25% of the US population, pediatric EHR functionality often is underdeveloped. When considering these systems for pediatric settings, particular attention should be focused on the highly specific data, task, and policy needs of pediatric practice.

The presence of functionality to support clinical tasks that are generally, if not uniquely, related to pediatrics should always be examined. Immunization management, including the ability to assess a patient's status or exchange data with an IIS, is highly desirable. Weight-based dosing and tracking of specialized growth parameters (eg, for Down syndrome, for preterm infants) are other functions that are often overlooked. Age-specific documentation and educational materials may be lacking or may require customization.

The data and terminology of an information system should suit the highly specific needs of pediatric practice. For example, units of measure should reflect the requisite data precision needs of pediatric patients. Options to display patient age in hours rather than years, months, or even days and weight in grams is critical to appropriate care in the neonatal period. Laboratory values should be accompanied by normative ranges for age. Patient identification must account for the frequent changes in names and numeric identifiers that may occur in infancy or during change of custody. Pediatric terminology, such as developmental milestones, type of cry, or characterization of stool, are often overlooked in information systems designed for adults.

Pediatric policy issues should also be reflected in the design of an information system. Authorization for the child or the child's parent(s), guardian(s), or other legal authority to view all, none, or

portions of a child's medical record should be enforced electronically as it would be for the paper medical record. This is particularly true for adolescent records, in which the need for granular awareness of EHR data elements by the pediatrician as well as privacy controls to restrict what a parent, guardian, or other legal authority may see, should be consistent with the relevant statute. Likewise, secondary use of patient data for public health, research, or commercial purposes should be allowed or restricted as appropriate.

Currently, no electronic medical home for the care of children exists. The electronic history of a child's care may be distributed across EHR systems, immunization registries, school health information systems, and specialty registries for rare conditions, trauma, or foster care. With the promise of HIEs as a conduit for data exchange, it may be possible to create a virtual medical home in the future. It is important that pediatricians work toward reducing the legislative, technologic, and cultural barriers to linking child health information systems without compromising the security or confidentiality of PHI.

Pediatricians should be actively involved in the acquisition and development of information technology to ensure that child-specific data and policy needs are addressed. Pediatricians should also be involved in national policy initiatives to ensure that health information systems are certified for pediatric use and integrated to support care that is child-centered.

CASE RESOLUTION

You speak with the head of the informatics committee. You learn that you have been asked to participate because of your understanding of physician workflow in the office setting and that you are intended to advocate for the highly specific data needs and policies associated with the pediatric population. You are expected to use your pediatric expertise and draw on your leadership experience to obtain stakeholder buy-in of information systems. Additionally, in collaboration with other pediatricians and physicians, you will work to improve the efficiency, effectiveness, and relevance of the EHR in supporting the physicians' work and working to achieve improved patient outcomes.

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CHAPTER 7

Counseling Families About Internet Use

Alan Tomines, MD

CASE STUDY

A 16-year-old girl is accompanied by her mother for a routine visit. The girl is doing well in school, is active in team sports, and has a small circle of friends who are well-known to her mother. The mother describes no new problems at home and no changes in behavior. However, the mother is concerned that her daughter "spends too much time on the computer."

Questions

1. What are the commonly used internet services?
2. What are the benefits and risks of the internet?
3. What strategies may be used to make the internet safer to use?
4. What signs may indicate that an adolescent is engaging in risky online behaviors?

The *internet* is a worldwide system of interconnected computer networks. At its inception, it was the exclusive domain of the military and academia; currently, the internet is a public gateway to electronic information, communication, and commercial services. The internet has profoundly changed the way we learn, work, play, and interact with others. It has become an integral part of the education and socialization of children, making it an influence of interest for parents, physicians, and researchers. The physician can provide pragmatic counsel to families that focuses on the benefits and risks of the internet, strategies for safer use, and assessment of online behavior in adolescents. The physician should also be prepared to discuss health information that families find on the internet.

A Brief History of the Internet

The internet began in the 1960s as the Advanced Research Projects Agency Network (ARPANET), a US Department of Defense project to share government-funded, university-based computer resources across a reliable communications network. Through the 1970s, ARPANET found acceptance with academics and researchers as a conduit for the exchange of scientific information, in large part because of the newly developed email technology for sending and receiving messages.

Recognizing the potential of the ARPANET, the National Science Foundation (NSF) began a parallel effort to connect the computer science departments at universities that were not affiliated with ARPANET. Initially called the Computer Science Network (CSNET) and later renamed NSF Network (NSFNET), this new network further expanded the exchange of scientific information. In 1990, ARPANET was retired, and many of its networks were absorbed into NSFNET. The resulting network, which was renamed the "Internet," extended its reach into the business sector and to international researchers but remained relatively inaccessible to the lay public.

During the early 1990s, the European Organization for Nuclear Research (known as CERN) developed protocols to facilitate the sharing of physics research data over the internet. These protocols allowed the sharing of computer files composed of text and images as documents that could be viewed using a special computer program called a "browser." This system of linked documents was collectively dubbed the World Wide Web or simply "the Web," with related collections of documents referred to as web pages or websites. In 1993, CERN made its work freely available, resulting in the rapid proliferation of publicly accessible commercial and personal websites—a model that has continued to the present day.

Internet Services and Concepts

Internet access usually is obtained through an *internet service provider* (ISP), a company that has an internet connection that it shares with consumers on a subscription basis. The most commonly used internet services are email and the Web. A person actively using an internet service is said to be "online." Use of the Web is sometimes referred to as *surfing* and is facilitated by *search engines*, such as Google and Bing, that use keywords or topics to find relevant documents, images, websites, or other services on the internet.

Internet services may be accessed by a wide range of computing devices, from traditional personal and laptop computers to mobile platforms, such as tablets and *smartphones* (cell phones that provide access to internet services). Smartphones and tablets access scaled-down versions of web-based content via specialized applications commonly referred to as "apps."

Because of their popularity in the pediatric age group, a few internet services are worthy of physicians' notice. *Web logs* (or *blogs*) are web-based journals. Like a traditional paper-based journal, a blog supports the written presentation of activities, thoughts, or feelings. A blog that is delivered using video usually is referred to as a *video blog* (or *vlog*). Blogs and vlogs may be public (available for anyone to read) or private (having restricted access).

Social networking websites, such as Facebook, Twitter, and Instagram, are similar in content to blogs and vlogs, with the added dimension that users are encouraged to create a network of online friends by establishing links to other users' social networking accounts. Blogs, vlogs, and social networking websites are examples of *asynchronous services* in which communication between users does not have to take place in real time and the content of which may be moderated and censored by the owner of the service for appropriateness.

By contrast, *chat rooms* are internet venues that permit the *synchronous* (ie, real-time) exchange of text messages between multiple simultaneous participants. Chat rooms as independent entities have largely been supplanted by other similar synchronous technologies, including direct messaging communication offered through social networking websites as well as instant messaging, a popular premium service often offered with smartphones. Although sometimes referred to as "text messaging," *instant messaging* (IM) is a more inclusive term that reflects the immediacy of interaction as well as the expansion of content exchanged to include multimedia, such as images or audio and video files.

The aggregate of synchronous and asynchronous social networking internet services is collectively referred to as *social media*. The ready accessibility of internet access, the portability of internet-ready devices, and the convenience of social media apps makes it possible to have a continuous online presence.

Internet Benefits and Access

The physician should be able to identify the benefits of internet use. The internet provides access to a wealth of educational resources and cultural experiences. Access to these resources allows children to exercise their reading, writing, information-seeking, and technology skills. The internet also provides the opportunity to easily communicate with family and friends. Additionally, children with common interests can use internet services to commiserate with and encourage other children. For example, the social networking websites Ben's Friends (www.bensfriends.org) and Rareshare (https://rareshare.org) connect patients with uncommon medical conditions to help them share their collective experiences.

The physician may also actively participate in reducing disparities in internet access. Internet use and access is correlated with socioeconomic status. Although currently most households have access to a computer with access to the internet, millions of individuals do not have access. The pediatrician may help families gain access to the internet by identifying institutions that provide safe online environments, such as libraries, community centers, and schools. As patient-centered internet-based health interventions are increasingly being studied as a supplement to traditional health care delivery, addressing disparities in internet access may help bridge gaps in care in underserved communities.

The physician should also be aware that children with disabilities may have difficulty using the internet without *assistive technology*, that is, hardware or software designed to improve the accessibility of computers. Children with visual impairment or blindness may be aided by the use of special software, including screen magnifiers, braille embossers, or *screen readers* (ie, software that uses a computer-generated voice to read email and web pages), although many websites are not compatible with screen readers. Children with hearing impairment or deafness may be aided by ensuring that their computers are set to provide visual cues rather than audio prompts; typically, such functionality is built into operating systems. Children with mobility or dexterity challenges may have difficulty using a traditional keyboard and mouse; alternative keyboards and pointing devices, computer touch screens, and tablet devices can be suggested as supporting technologies. Pointing devices that use sound or infrared beams, as well as software that responds to the spoken word, may be viable alternatives in cases in which manual control is not possible.

Internet Threats

Although the internet has many benefits, being online entails some risks. The physician should be able to inform parents and guardians about the threats posed by the internet.

To understand internet threats, it is helpful to recognize that the internet has neutral properties that do not cause threats but that allow them to exist. First, the internet is anonymous: People may not be who they represent themselves to be. Second, the internet is interactive: Unlike traditional media (eg, newspapers, radio, television), the internet user may have real-time interactions with another person, or with sophisticated computer programs that respond as if human. Third, the internet has few restrictions: Anyone can put almost anything on the internet, without regard to credibility or appropriateness. Finally, the internet is public and permanent: Although information on a website may be removed, it is possible for anyone who visits a website to make an electronic copy of what is there, and many websites are archived and may be retrievable from websites, such as the Internet Archive (http://archive.org), long after their removal from internet search engines.

Although these properties of the internet are neutral, they enable some of the most common internet threats: exposure to strangers and/or predators; interpersonal victimization; exposure to pornography; and participation in online gaming, gambling, and shopping.

The anonymity and interactivity of the internet enables online predators. More than one-third of adolescents online have "friends"

whom they have never met in person. Approximately three-fifths of adolescents active online have received an instant message or email from a stranger, and approximately 1 in 6 has been contacted by someone who made them feel scared or uncomfortable. More than 90% of teenagers have shared personal information about themselves online, including name, birth date, interests, and contact information.

Online interpersonal victimization is the receipt of harassment or unwanted sexual attention over the internet. One-fifth of children have reported being victimized; 1 factor that places individuals at high risk for victimization is talking about sex with someone online. *Cyberbullying* is a specific type of online interpersonal victimization consisting of receipt of electronic communications that are harmful or threatening. Cyberbullying may be as prevalent online as "traditional" bullying, with nearly one-fifth of middle school–age children reporting that they had been cyberbullied at least once in the previous 12 months. Approximately 88% of teenagers have witnessed other people being mean or cruel online, with 21% saying that they have joined in.

Although children may be individually targeted by strangers or cyberbullies, they may also passively encounter undesired internet content. More than 40% of children reported having been exposed to pornography online, and nearly two-thirds of those children described this exposure as unwanted. In adolescents between the ages of 15 and 17 years, more than 70% reported accidentally being exposed to online pornography, with a risk factor for exposure being the downloading of images.

Sexting is the exchange of sexually explicit text, images, or multimedia, generally via IM. Sexting sits at the convergence of pornography and cyberbullying, with the added danger that some adolescents may not perceive sexting as harmful or threatening. In some jurisdictions, minors who have participated in sexting have been charged with possessing child pornography.

In addition to the aforementioned threats, recent studies point to the internet and digital media use as having a role in addictive behavior and attention-deficit/hyperactivity disorder as well as in detracting from healthy behaviors, such as physical activity and adequate sleep. With the wide variety of benefits of and threats posed by the internet, the physician should be prepared to provide parents and guardians with strategies for appropriate and safe internet use.

Strategies for Appropriate Internet Use

The physician may assist parents and guardians with promoting appropriate internet use by informing them of the benefits and threats, helping them set guidelines for screen time and content, and encouraging them to be active participants with their children online. Parents or guardians who may not be technically savvy or may require basic instruction on internet use may be advised of the availability of classes offered by libraries, schools, and community groups.

The American Academy of Pediatrics (AAP) has provided age-specific guidance for the use of digital media, including the internet. These recommendations include the avoidance of most screen media for children younger than 18 months; limiting screen use to 1 hour per day for children ages 2 through 5 years; and consistent time limits for children age 6 years and older, specifically identifying activities that are not allowed. The AAP offers a Family Media Plan tool (www.healthychildren.org/English/media/Pages/default.aspx) to assist parents and guardians in creating developmentally appropriate plans for managing digital media use.

By sharing time online, parents and guardians can promote and model responsible internet behavior. These adults should talk with their children about what they see together on the internet and encourage children to share what they have experienced when online alone, whether good or bad. Placing the computer or other internet-enabled device shared by the family in a public location in the home will encourage the idea that the internet is a shared experience; however, caregivers should be aware that mobile devices allow children to access the internet independently and covertly.

Parents and guardians should set and enforce house rules for internet behavior. Children should be encouraged to be good citizens, including not doing anything that may be hurtful to others and not plagiarizing information that they find freely on the internet. Children should not communicate with or plan to meet strangers known only to them through the internet, nor should they respond to messages that are unsolicited or that make them feel uncomfortable. Children should not share personal information or pictures with others on the internet, nor should they download files from the internet. For older children, safety pledges can be used as formal agreements of acceptable use.

To facilitate parental or other caregiver oversight of internet use, the physician should advise that computers and mobile devices may be configured to allow internet access only during certain hours of the day and to disable access to the internet after a specified amount of time has elapsed. As possible, children should be provided with a separate account to access devices and the internet. Having a separate account promotes autonomy for older children while allowing parents or guardians to restrict internet content. Monitoring software automates tracking of internet usage by creating a reviewable record of websites and images viewed, messages sent and received, and even individual keystrokes entered. The potential benefits of monitoring software should be weighed against the invasion of the child's privacy, and parents and guardians should understand that some children are savvy enough to erase their internet browsing history; consequently, the absence of a web browsing history may be a cause for suspicion. Parents and guardians should also regularly monitor IM activity on smartphones.

Strategies for Safer Internet Use

Although encouraging appropriate use and behavior is important to enjoying the benefits of the internet, the physician should also recommend the use of internet safety tools to protect against inappropriate use and external threats.

Software to protect malware is not directly targeted to children, but it is something about which parents and guardians should be

aware. Malware generally includes *viruses* and *worms* (ie, software programs that can corrupt the information saved on a computer), *spyware* (ie, software that tracks internet activity and sends this information to another person), and *pop-ups* (ie, a new browser window that may contain marketing or other undesired content). Viruses and worms are generally downloaded as attachments in email, whereas spyware and pop-ups are introduced by surfing the Web. Attempts should be made to protect against *spam* (ie, unsolicited email) as well, which may contain undesired content or solicitations.

Filters are special computer programs that allow the presentation of acceptable internet content and that block content deemed to be inappropriate. Filtering may use 1 or more of the following methods: "blacklists" of websites that are specifically blocked; "white lists" of websites that are specifically permitted; the blocking of specific words or terms; and the maturing technology of blocking suspicious image content. Filters are neither perfectly specific nor perfectly sensitive and may require adjustment by the parent or guardian to achieve an acceptable level of filtering. Parents and guardians may contact their ISP to enable *server-side filtering* (ie, filtering of content before it enters the home). If server-side filtering is too restrictive for some members of the household or not sufficiently restrictive for others, a *client-side filtering* approach may be considered, in which filtering software is installed directly on computers or mobile devices. Client-side filters work with standard web browsers, although special child-oriented web browsers may be acquired that have client-side filtering built in.

When a child encounters inappropriate internet content or messages that are hurtful or distressing, parents and guardians should alert their ISP as well as the owner of the website on which the content was or messages were discovered. As appropriate, the parent or guardian should also contact the appropriate legal authorities and the National Center for Missing & Exploited Children (www.missingkids.com). Commercial websites that collect personal information from children younger than 13 years are required to follow the Children's Online Privacy Protection Act of 1998, which is enforced by the Federal Trade Commission. According to this law, internet website operators must post their policy indicating what personal information is collected, how that information will be used, and if that information will be shared with a third party. Parents or guardians must consent to the collection and use of personal information and may revoke this consent at any time.

Additional internet safety information is available to families through reputable web-based resources, such as the Federal Trade Commission resource OnGuardOnline (www.onguardonline.gov), the National Center for Missing & Exploited Children's NetSmartz Workshop (www.netsmartz.org), iKeepSafe (www.ikeepsafe.org), and INOBTR ("I Know Better") (www.inobtr.org). Parents and guardians should also be aware of other venues in which their children may access the internet, such as schools, libraries, and friends' homes, and they should find out what internet safety policies and technologies have been instituted in these environments.

Adolescents on the Internet

Most adolescents have access to the internet from home, and many more may gain access to the internet at school or at a friend's house. Additionally, 95% of adolescents report that they have access to a smartphone, and 45% report that they have a nearly continuous online presence. Parents and guardians should be aware that adolescents who have excessively restrictive internet rules at home are more likely to attempt internet access outside the home, where it may be more difficult to monitor their activity.

Adolescents have mixed views on the effect of the internet, specifically social media, on their lives. Approximately 45% of adolescents believe that social media has neither a positive nor a negative effect, approximately 30% describe its effect as mostly positive, and nearly 25% describe its effect as mostly negative. Open parent-/guardian-child communication about internet use should be encouraged so that adolescents feel that they can discuss what they see on the internet with their parent or guardian without jeopardizing their internet access privileges.

Adolescents may engage in risky online behaviors, including communicating with and planning to meet strangers in person. Based on review of past cases, the Federal Bureau of Investigation has identified specific behaviors that may indicate a child is engaging in risky online behaviors, including spending several hours online, especially at night; having pornographic images on the computer; turning the monitor off or quickly changing the screen when a parent or other caregiver enters the room; and using unrecognized user names or accounts. Other offline behaviors that should arouse suspicion include telephone calls from unknown adults, outgoing calls to unrecognized telephone numbers, gifts or packages received, and unexplained credit card activity.

The physician should consider addressing online activities in the adolescent psychosocial review of systems. Asking adolescents about online activities may unveil risky online behaviors or provide an opportunity to discuss concerns about their health and well-being. Nearly one-third of adolescents have searched the internet for health information, often related to sex and sexually transmitted infections, nutrition, and exercise and fitness. Adolescent girls in particular have a tendency to search for information on physical abuse, sexual abuse, and dating violence as well. Online activities worthy of inquiry include health topics searched for on the internet, which social networking accounts the adolescent has, sharing personal information on the internet, communicating with strangers, meeting people known only via the internet, and engaging in (or being a victim of) cyberbullying or sexting. Adolescents should also be reminded that the internet is not private and that colleges and employers may discover information about the adolescent on what appear to be "private" social networking pages.

Health Information on the Internet

Patients regard physicians as the preferred and most trusted source for health information; however, patients increasingly seek out health information on the internet before, or sometimes in lieu of,

consulting with their physician. It is important to remind families that health information on the internet may be outdated, incomplete, incorrect, intentionally misleading, or easily misinterpreted. When a patient has questions about information found on the internet, the physician should take care not to disregard the information outright. These inquiries provide opportunities to educate the patient and address issues of concern, and the patient may value the physician's opinion of the information.

The physician may support patients by suggesting evidence-based health information resources on the internet, such as the AAP's official website for parents (www.HealthyChildren.org); the US National Library of Medicine website MedlinePlus (www.medlineplus.gov); the Centers for Disease Control and Prevention (www.cdc.gov); and the US Department of Health and Human Services (https://healthfinder.gov). The specialist should be prepared to identify online information sources and support groups, particularly for rare, chronic, or debilitating conditions. The physician should caution families caring for children with special medical conditions about the characteristics of less reliable online resources or support groups, which may include novel or alternative treatment regimens, advice to stop treatment, or charging of fees for participation or treatment.

CASE RESOLUTION

The pediatrician learns that the adolescent uses her laptop computer for 1 to 2 hours every afternoon to complete her homework assignments and is on the internet for an additional 2 to 3 hours every evening streaming videos on YouTube, posting images and thoughts to her Instagram and Snapchat accounts, and occasionally checking her Facebook page. The pediatrician advises the girl that, for safety reasons, personal information should never be shared over the internet, adding that colleges and employers often research prospective candidates online. The pediatrician also asks whether the patient has received, witnessed, or participated in hurtful or distressing communications or imagery online. With both the mother and daughter present, the pediatrician discusses the option of drafting a parent-child contract that clearly establishes the rules for acceptable internet use in and out of the home, including appropriate time limits. The pediatrician also directs the mother to internet-based resources for safeguarding the home environment and mobile devices, as well as a workshop at the local library on internet security.

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CHAPTER 8

Cultural Competency Issues in Pediatrics

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CASE STUDY

You are seeing AJ, a 12-year-old Mexican American boy, for a well-child visit. His mother speaks Spanish and "a little" English, is single, and works full time in motel custodial services. After school and during summers, AJ is cared for by his 17-year-old brother and his maternal grandmother, who lives a block away. AJ's weight and body mass index are well above the 95th percentile for his age. When discussing his diet, you learn that his mother buys packaged foods that he can make for himself when she is away. She is concerned that he will not eat if she does not buy the processed, fatty foods he likes. Additionally, these types of foods are more plentiful than healthier options at the local market at which she shops. AJ sometimes eats at his grandmother's home, but she is elderly and does not cook much anymore. When discussing physical activity, AJ states that he wants to play soccer. His mother is concerned about this, however, because he often complains of headaches and stomachaches when it is time for practice, and she does not want to buy the equipment if he will quit after a few weeks, as has happened in the past.

As is your practice with all adolescents, you ask to speak with AJ alone. During your assessment, you learn that he is attracted to boys but has not shared this information with anyone. He is certain that his brother will not approve and that his mother will be heartbroken. He is sometimes teased at school because he is "not tough enough," and he fears some of the bigger bullies might try to jump him if he hangs around after school to participate in any after-school sports activities.

Questions

1. What is the definition of culture?
2. What is cultural competence? What is cultural destructiveness?
3. What is meant by unconscious bias?
4. Why is it important to use a certified interpreter when talking to the parent with limited English proficiency? When is it appropriate for the pediatric patient to interpret for their parent?
5. How does understanding the perspective of the patient and the parent affect medical decision making?

The provision of culturally competent care is no less important for pediatric patients than adult patients. Those who provide health care to children face many important issues concerning culturally competent care, including health disparities and health care disparities based on socioeconomic status, ethnicity and/or racial identity, sexual orientation, and gender identity. Many issues of cultural competency, health disparities, and approaches to cross-cultural care are similar across minority populations in the United States, including some rural white populations.

Definition of Culture

Culture is a set of meanings, norms, beliefs, and values shared by a group of people. It is dynamic and evolves over time and with each successive generation. Culture encompasses a body of learned behaviors and perspectives that serve as a template to shape and orient future behaviors and perspectives from generation to generation and as novel situations emerge. It shapes how and what symptoms are expressed and influences the meaning that individuals attribute to symptoms, including one's beliefs about the causes, effects, and potential remedies for these symptoms. Culture is a broad category that includes not only race and ethnicity but also sexual orientation, gender roles, gender identity, socioeconomic status, nationality, and other group affiliations. The interaction between the culture of the patient and family and that of the physician is often significant and can result in bias in both assessment and treatment. These biases, in turn, can contribute to health and health care disparities.

Health Disparities

Health disparities are differences in health outcomes across different groups. *Health care disparities*, as defined by the Institute of Medicine (now the Health and Medicine division of the National Academies) in the document *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care,* are "racial or ethnic differences in the quality of health care that are not due to access-related factors or clinical needs, preferences, and appropriateness of intervention." Health disparities and health care disparities exist within the United States and particularly affect minority populations. Although health disparities may be caused by many social determinants of health, such as socioeconomic status and access to safe neighborhoods, healthy food, and health care, health care disparities are directly related to what happens to certain patients in the health care system after they have accessed care. Addressing health disparities moves medicine and society closer to *health equity,* which is achieved, as defined by Braveman et al, "when everyone has a fair and just opportunity to be as healthy as possible."

Latinx is a gender-neutral term that refers to individuals of Latin American heritage. Latinx children in the United States face significant health and health care disparities. (Throughout this chapter the term Hispanic is used for information reported from any study in which that term was used.) The Hispanic population has among the highest prevalence of overweight in children, but American Indian/Alaska Native children having the highest rates of overweight, at nearly one-third of that population. Additionally, in the United States Hispanic children also have a lower fitness level and watch more television than white children. The reasons behind these disparities are complex and multifactorial. Many ethnic minorities and limited English proficiency (LEP) groups also face disparities in the health care they receive. For example, for minority groups the duration of their routine well-child visits is shorter and Latinx children are less likely than white children to receive counseling at these visits.

In addition to these examples of lack of access to quality health care, many social, political, and cultural elements contribute to health disparities observed in certain ethnic groups. Evidence exists to indicate that these social determinants have a more significant effect on health than medical care does (see Chapter 141). Although physicians can effectively address the social determinants of health through activism and advocacy, it may be difficult to do so on an individual patient care level. Nevertheless, it is important to understand these issues and how they may contribute to patients' health outcomes. For example, lack of access to quality, low-cost foods in one's neighborhood, lack of transportation, advertising practices that target low-income communities, and lack of access to safe playgrounds are examples of social determinants that contribute to obesity. It is also essential to understand the influence of culture on patients' health beliefs, health behavior, and health status. Cultural issues are further discussed later in this chapter.

Finally, acculturation is also likely to affect health, health beliefs, and health behaviors. Second-generation Hispanic adolescents are twice as likely as first-generation Hispanic adolescents to have obesity or overweight. Similar findings have been observed in other populations (eg, Americans of Asian descent). Acculturation across generations in Hispanic communities has been associated with decreased fruit and vegetable consumption, increased soda consumption, and decreased physical activity. These effects of acculturation have been shown in other immigrant groups as well. Acculturation is a complex variable in relation to pediatric obesity, however. For example, in 1 study, Mexican American mothers who were less acculturated had children with higher body mass indices.

Cultural Competence

Physicians who strive for cultural competence attempt to minimize their bias and seek to incorporate cultural assets into their work with patients. Cultural competence is a continuum (Figure 8.1). *Cultural destructiveness*, the least developed state along that continuum, comprises attitudes and practices that are meant to be harmful to cultures and individuals within the particular culture. Physicians at this level may overtly discriminate against individuals based on their culture (eg, intentionally making homophobic, racist, or sexist remarks to colleagues). Physicians who have *cultural incapacity* do not overtly discriminate but lack the ability and willingness to recognize and intervene when discrimination happens. As a result, they ultimately reinforce culturally oppressive behaviors and policies. In the *cultural blindness* phase, an individual believes that culture makes no difference and that all people are the same. This viewpoint ignores cultural strengths, encourages assimilation, and often results in blaming the victims of racial injustices for their problems. Physicians at this stage may have difficulty believing in the validity of health disparities, despite the enormous body of evidence supporting the existence of such disparities. Although these physicians strive to give quality care to everyone, they do not recognize culture-specific experiences that affect patients' health, such as poverty or violence based on race, sexual orientation, or

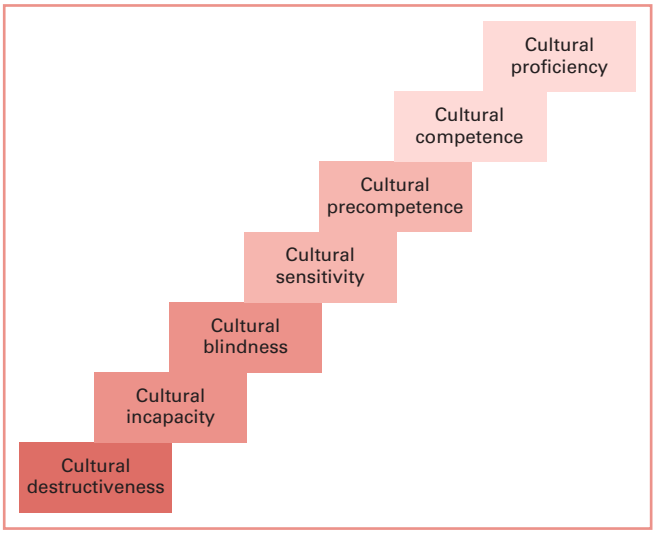

Figure 8.1. Steps in achieving cultural proficiency.

gender, and they miss opportunities to incorporate culturally relevant strengths into treatment, such as collaboration with traditional healers, extended family, or faith-based organizations. *Cultural precompetence* is characterized by a willingness to deliver quality services and a commitment to civil rights but a lack of knowledge and experience to implement culturally relevant services. Culturally pre-competent physicians often struggle with knowledge that disparities exist and that perhaps they continue to contribute to them but are at a loss as to what to do about it. In contrast, physicians at the stage of *cultural competence* seek to expand their cultural knowledge and resources, often in consultation with culturally diverse communities. They also continuously self-assess and adapt traditional service models to enhance care for culturally diverse patients. Using native culture-based talking circles with American Indian youth to improve their understanding of obesity is an example of working at this stage of cultural competence. Finally, physicians who exhibit *cultural proficiency* hold cultural diversity in highest esteem and continuously advocate for increased cultural competence throughout the system of care. It is important to recognize that physicians move back and forth along this continuum dynamically, influenced by their own experiences. For example, physicians who identify with being in the culturally competent phase when working with Latinx patients may find themselves having cultural incapacity when working with gay or lesbian patients.

Another helpful model is the concept of *cultural humility*, which is a process of self-reflection and commitment to a lifelong learning process, thereby engaging the physician in an ongoing courageous and honest process of self-critique and self-awareness. Both the cultural competence model and the cultural humility model reflect cultural competency as a process rather than an end result or a fixed state.

Communication

Initially, during every clinical visit, it is important to maximize communication with the patient and the parent (see Chapters 2, 3, and 4). Effective communication results in an improved physician-patient relationship, treatment adherence, and health outcomes. Poor communication may have negative consequences. Patients with LEP, in particular, have increased barriers to health care, decreased health quality, and decreased health status. In a Joint Commission study involving 6 hospitals, researchers found that patients with LEP were at increased risk for iatrogenic harm. In contrast, use of interpreters is associated with increased follow-up with preventive and primary care services. Ideally, a trained medical interpreter should be available to communicate with patients or parents who do not speak English. Although it happens often in clinical practice, it is inappropriate to rely on the patient to interpret for the parent. It is clearly a difficult position for a child or adolescent to interpret health information for a parent. It is not guaranteed that the patient understands what the physician is communicating or that the patient is interpreting correctly for the parent. It also disturbs the power balance between parent and child. Strategies for using interpreters are provided in Box 8.1.

Box 8.1. Strategies for Using an Interpreter in the Clinical Visit

- Talk with the interpreter briefly before the interview to discuss overall goals for the interview and ground rules (eg, use word-for-word interpretation). If using a certified medical interpreter via telephone, have a brief discussion about the goals for the interview.
- Give the interpreter and the patient permission to ask questions about terminology with which they may be unfamiliar.
- Use nonverbal behaviors, such as eye contact, nodding, and facial expressions, to signal to the patient that the physician understands what is being communicated.
- Speak directly to the patient and address the patient in the first person.
- Use short, simple statements and speak on 1 topic at a time.
- Avoid medical jargon and ambiguous statements.
- Meet briefly with the interpreter after the interview to confirm pertinent information, ask about cultural information, and discuss feedback. Do this with telephone interpreters as well.
- Remember that interpreters are not medical professionals. Therefore, consider information volunteered by interpreters as being reliable as collateral information provided by other individuals who are not health professionals.

Unconscious Bias

In addition to ensuring effective communication, it is important for the physician to address the unconscious biases that the physician may have about a patient. Although few health professionals intentionally discriminate based on culture, studies suggest that physicians are likely to have unconscious biases that can significantly affect patient care.

Physicians can take steps to manage unconscious bias. It is essential to first acknowledge that bias does exist in the health care system and within the lived experience of patients as well as physicians. It is good practice for health professionals to explore the Project Implicit website (https://implicit.harvard.edu/implicit) and take the online tests designed to detect bias across various cultural dimensions, including race, sex, gender, and sexual orientation. Most people who take these tests quickly realize that they carry biases they had no idea existed within themselves. For many, acknowledging their own biases may be the most difficult step. The next step is to work toward replacing one's own biases with positive and realistic associations about other groups. For example, seeking out dialogue and companionship with people culturally different from oneself can help replace one's negative assumptions with more positive associations. Finally, it is important to be mindful of the potential influence of unconscious bias on medical decision making, whether treating a patient of similar background to the physician or a patient of a quite different background. It is essential to consider cultural context; however, it is also important to be aware that each patient is a unique individual. In any situation in which bias may be present, the physician should speak less and listen more, striving to avoid assumptions.

Eliciting Patients' Perspectives

Optimization of clinical collaboration is dependent on each stakeholder—patient, family, and physician—having an opportunity to express their understanding of the health issue in question. Typically, however, the physician obtains the patient history with limited consideration of the patient's and family's beliefs about the health problem. Difficulties may arise if the patient or a family member disagrees with the physician's explanations of the illness. In many cultures, openly disagreeing with a physician's assessment and treatment recommendations is considered disrespectful. Instead, the patient and family may acknowledge the physician's status by expressing agreement but maintain their own ideas about how to address the issue. For example, although a parent may report the intention to follow through with the physician's recommendation to change to a healthier diet to improve the health of the child, the parent may continue to purchase less healthy ready-made foods because of real or perceived difficulties getting healthier foods given the parent's long work hours and the lack of healthy food in the family's neighborhood. The physician may characterize obesity as a primarily biologic problem, whereas the parent may view the condition primarily as a problem of access and time.

Furthermore, the parent may not perceive the child's overweight status as a problem at all. The relationship of pediatric obesity to cultural ideals and norms around food, eating, and parenting is complex. Some evidence in ethnographic studies shows that, in some Latinx cultures, feeding children and especially giving "treats" is a means of showing love. A parent or guardian with a child who is a so-called healthy eater may not want to limit the child's enjoyment of food. Additionally, body size ideals vary across communities, and some evidence indicates that in some Latinx communities children who meet criteria for overweight are considered more attractive and healthier than thinner children, who may be considered frail. Poverty and the experience of food scarcity can further exacerbate overeating during times when food is more accessible. Finally, particularly when other friends or family members offer food to a child, it may be considered socially unacceptable for the parent to refuse or criticize the type of food being offered. Understanding such cultural norms can be helpful in treating individual patients. It is important to remember, however, that particular individuals and families have their own cultural norms that may or may not be consistent with others in their ethnic group.

Conflicts in health beliefs between the physician and the patient and/or family may result in treatment nonadherence and dropout. It is important that the physician and the patient and/or family discuss their respective health perspectives. The better the physician's understanding of the health beliefs of the patient and family, the more effectively the physician can address differences and build on common ground. Likewise, patients and families may feel a greater level of comfort with a physician's recommendations if their questions and concerns about the physician's perspectives are addressed. The questions in Box 8.2 can help a physician further understand the health beliefs of the patient and family.

Decision Making

It is also important for the physician to understand how the patient or family makes medical decisions. Many physicians look to a child's parent or guardian as the primary decision maker. This process may be culturally influenced, however. Parents or guardians from strongly collectivistic cultures, in which the needs and priorities of the group supersede those of the individual, may wish to involve others (eg, senior family members, spiritual leaders, clan leaders) in health care decision making. Failure on the part of the physician to allow the inclusion of these persons in the decision making process may result in the parent or guardian feeling forced into a decision, may precipitate conflict within the family, and may result in the family or community blaming the parent or guardian should a bad outcome occur. Suggested questions for facilitating a discussion about decision making are presented in Box 8.2.

Sexual Orientation and Gender Identity

At any clinic visit, it is extremely important for the physician to remain nonjudgmental and be supportive of the patient's sexual orientation and gender identity development. (See

Box 8.2. What to Ask

General Questions

- About which problem or problems are you most concerned?
- What do you think has caused the problem?
- What are your concerns about this problem? How does it affect you and your child?
- What treatments do you think might work for it?
- What have you done in the past? How satisfied were you with the results?
- What are your goals for treatment?
- What is your understanding of the treatment offered? What are your concerns about it? What are the barriers for completing or carrying out the treatment?

Health Issues Identified by the Physician

- What do you think about the concerns that I have raised with you (ie, the problems the physician has identified [eg, obesity])?
- Have you been told about this concern before? If so, what is your understanding of it?

Decision Making

- How do you usually make decisions about health care?
- Do you involve anyone else in that process? Who? What are their roles?
- Who usually makes the final decision?
- How comfortable are you with using that process to make decisions about your child's current situation?

Chapters 57 and 150, respectively, for suggestions on providing culturally competent care around sexual orientation and gender identity and on addressing bullying.) Two helpful resources are the Fenway Institute National LGBT Health Education Center (www.lgbthealtheducation.org/lgbt-education/learning-modules/) and the Family Acceptance Project (https://family-project.sfsu.edu).

As the result of inequitable treatment, sexual minority individuals experience significant health disparities. Discrimination, bullying, and abuse can result in mental health issues, such as depressive disorders, posttraumatic stress disorder, suicidality, and substance use. Individuals who are lesbian, gay, bisexual, transgender, or questioning (LGBTQ+) also have more barriers to access health services than heterosexual cisgender individuals, resulting in lower rates of screening and preventive services. (A *cisgender* person is one whose gender identity or expression matches the cultural norm for the person's biologic sex.) Youth who are LGBTQ+ are also more likely to face family alienation and homelessness. Disclosure of sexual orientation and physician attitude are important mediating factors to heath care experiences of LGBTQ+ individuals; however, 90% of youth in 1 study reported having reservations about disclosing to their physician. This underscores the importance of physician training on facilitating these important conversations.

It is also important to examine the intersectionality of ethnicity, sexual orientation, and gender identity. For example, the National Longitudinal Study of Adolescent Health, in which 20,000 adolescents were surveyed, indicated that male and female Hispanic adolescents were more likely to report same-sex romantic attraction than their peers of other ethnic groups. This difference was significant compared with white and Asian peers. Additionally, male and female Latinx adolescents were more likely than their peers to be victims of violence. These findings show that issues of sexual minority groups and bullying are important to consider in addressing adolescent health disparities in culturally diverse communities in the United States.

It is also important to understand the patient's sexual orientation in the context of the patient's family and ethnic community. For example, in some traditional communities, such as some American Indian tribes, certain sexual minorities (eg, nonbinary or "two-spirit" individuals) are accepted in the community and considered to possess certain spiritual gifts. Although LGBTQ+ youth in Latinx families do face challenges, particularly in situations in which antigay religious views are of strong influence, strong cultural identity can serve as a grounding influence for LGBTQ+ individuals. For example, in 1 study, young urban Hispanic men who have sex with men were less likely to engage in risky sexual behavior if they were connected to their ethnic community.

CASE RESOLUTION

While speaking with AJ alone, you express support for his early sexual identity development, identify safe adults in his life with whom he can discuss his feelings and concerns, and identify community resources for LGBTQ+ individuals. When AJ's mother returns to the room, you also discuss AJ's and his mother's perspectives about food, his weight, and his activity level, using a medically trained interpreter to ensure clear communication with his mother. You identify some of this family's strengths: AJ's mother's desire to help him be healthier; AJ's relationship with his grandmother, who cooks healthy traditional foods; and AJ's supportive relationship with his older brother. After discussion, the patient decides that he would like to learn to cook from his grandmother and will commit to cooking a family dinner once a week, which delights his mother. His brother has also agreed to take him to soccer practice and games for a neighborhood soccer team. AJ likes this idea, because he feels safe from bullies with his brother present and feels that soccer will help him be stronger and more confident. You arrange for a follow-up visit in several months to check in with AJ and his mother about their progress and to brainstorm about further interventions. This will include 1-on-1 time with AJ and further discussion of his sexuality.

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CHAPTER 9

Global Child Health

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CASE STUDY

You are watching television when the programming is interrupted by breaking news that a severe earthquake has struck a developing country you have recently visited. You wonder if and how you could become involved in efforts to help the country respond to the disaster, prevent diseases, and rebuild its health care infrastructure.

Questions

1. What are the global trends in childhood disease and mortality? How does this compare with the United States?
2. What is global health?
3. What is the role of the pediatrician in global health?
4. What are the key organizations in global health with which pediatricians work?
5. How can the pediatrician carry out international work in an ethical and effective manner?
6. What are useful global health resources?

Background

Worldwide, an estimated 5.3 million children younger than 5 years of age died in 2018, for an average of nearly 15,000 children dying each day (Figure 9.1). This represents a 58% reduction from the 12.6 million deaths of children younger than 5 years of age estimated in 1990. Even so, significant disparities in child mortality persist and have become increasingly concentrated geographically, with specific regions of the world bearing a disproportionate burden. The continents of Africa and Asia combined account for 86% of all child deaths, with one-third of these deaths occurring in South Asia and half in sub-Saharan Africa. Less than 1% of deaths occur in high-income countries.

Nearly one-third of all child deaths worldwide were caused by 3 communicable diseases: pneumonia (16%), diarrhea (8%), and malaria (5%). Most of these lives could be saved through increased access to low-cost prevention and treatment measures, including

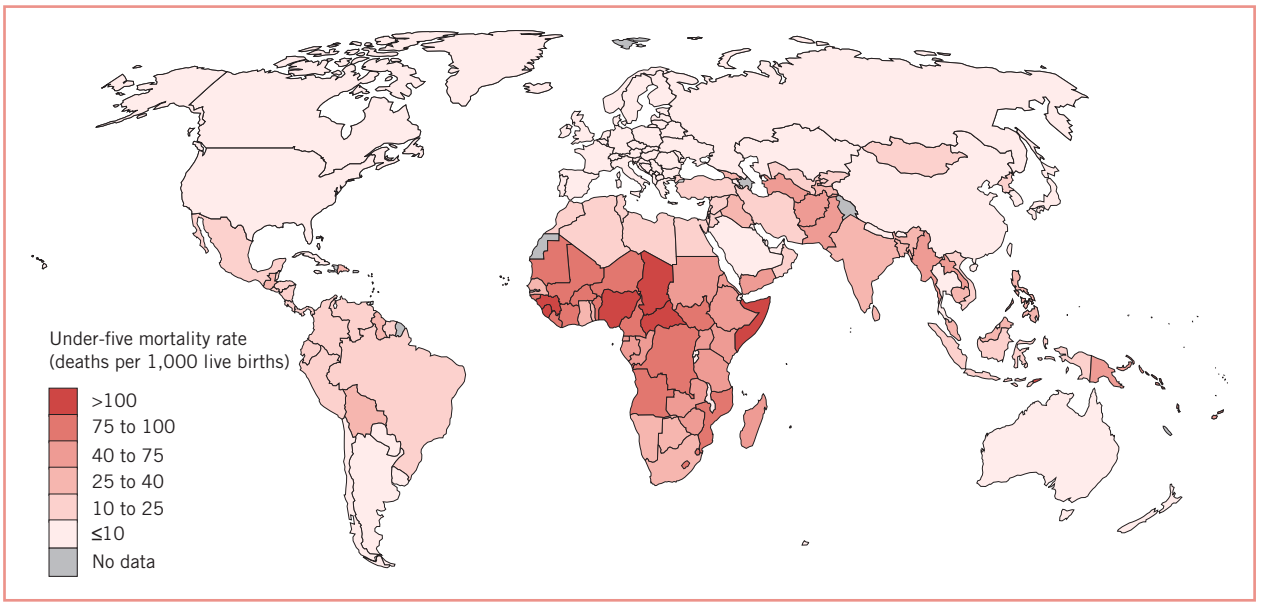

Figure 9.1. Mortality rates for children younger than 5 years in 2018.
Reprinted with permission from United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). *Levels & Trends in Child Mortality: Report 2019. Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation.* New York, NY: United Nations Children's Fund; 2019.

antibiotics for acute respiratory infections, oral rehydration therapy for diarrhea, immunizations to protect against pneumococcal pneumonia and diarrhea caused by rotavirus gastroenteritis, and the use of insecticide-treated mosquito nets and appropriate drugs for malaria.

Undernutrition is an underlying cause of at least one-third of all deaths in children younger than 5 years. Reducing chronic and acute undernutrition would have a substantial effect on reducing child mortality. Furthermore, improved coverage of specific nutritional interventions, such as early and exclusive breastfeeding, are cost-effective and reduce the prevalence of pneumonia and diarrhea.

The first month after birth is a perilous phase for a child's survival, with an estimated 47% of deaths in children younger than 5 years occurring during this period. Most of these deaths occur at home in the first postnatal week as the result of preterm birth (18%); intrapartum-related complications, such as birth asphyxia (12%); and neonatal sepsis (7%). Thus, improving neonatal care is essential to the goal of improving child health. Increased access to basic, inexpensive interventions is necessary to reduce neonatal mortality rates globally, including delivery by skilled birth attendants, hygienic umbilical cord care, and the training of community health workers to assess and begin early treatment for neonatal infections.

Mortality among young children aged 5 through 14 years is lower than that of children younger than 5 years (7.2 deaths per 1,000 live births and 39 deaths per 1,000 live births, respectively). Decreases in mortality for these older children and adolescents have slowed since the year 2000, however. In 2017 an estimated 0.9 million children 5 through 14 years died, which represents approximately 2,465 deaths each day. Most deaths among these children occurred in sub-Saharan Africa (54%) and Southern Asia (25%). Injuries accounted for a larger proportion of deaths (30%) among these older children than among children younger than 5 years, with drowning and road injuries causing 14% of deaths in the older age group. Leading causes of death among adolescents ages 10 through 19 years include road injury, HIV, suicide, lower respiratory infections, and interpersonal violence.

Box 9.1. United Nations Sustainable Development Goals[a]

1. End poverty in all its forms everywhere
2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture
3. Ensure healthy lives and promote well-being for all at all ages
4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all
5. Achieve gender equality and empower all women and girls
6. Ensure availability and sustainable management of water and sanitation for all
7. Ensure access to affordable, reliable, sustainable and modern energy for all
8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all
9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
10. Reduce inequality within and among countries
11. Make cities and human settlements inclusive, safe, resilient and sustainable
12. Ensure sustainable consumption and production patterns
13. Take urgent action to combat climate change and its impacts
14. Conserve and sustainably use the oceans, seas and marine resources for sustainable development
15. Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
17. Strengthen the means of implementation and revitalize the global partnership for sustainable development

[a] These goals were developed and signed by all United Nations member countries in 2015. There are 17 goals with 169 targets (with 1 specific goal for health that includes 13 health goal targets) and a series of measurable indicators for each target.

Sustainable Development Goals

In 2015, world leaders agreed to the 17 Sustainable Development Goals (SDGs) for improving global well-being by 2030. The SDGs were built on lessons learned from the 8 Millennium Development Goals (MDGs), which were specific, measurable targets set by the United Nations in 2000 to eradicate poverty, hunger, illiteracy, and disease by 2015. Progress toward meeting the MDGs has been significant, although uneven, with the poorest and most disadvantaged countries as well as marginalized communities and social groups within developed countries not attaining these goals.

The SDGs aim to address the underlying determinants of poverty and poor health in a sustainable manner by expanding its goals to address the systems-based, underlying socioeconomic, political, and environmental factors. The 17 interconnected SDGs are comprehensive and apply universally to all nations, both developed and developing (Box 9.1).

The third SDG (SDG-3) specifically focuses on population health, to "ensure healthy lives and promote well-being for all at all ages." Although the MDGs included targeted relative reductions in mortality (eg, reduce under-5 mortality by two-thirds), the SDG-3 sets absolute targets to end preventable deaths of neonates in particular and other children younger than 5 years of age. Specifically, these more equitable goals call on all countries to reduce neonatal mortality to no more than 12 deaths per 1,000 live births and under-5 mortality to no more than 25 deaths per 1,000 live births by 2030.

Inequities in Health

Significant disparities exist in child health. Sub-Saharan Africa grapples with a high child mortality rate (ie, 76 per 1,000 live births in 2017); that is, 1 in 13 children in that region dies before 5 years of age. In comparison, Western European countries have an under-5-year mortality rate of 4 deaths per 1,000 live births, and in

high-income countries fewer than 5 per 1,000 children die before their fifth birthday.

In 2017, an estimated 82% of all the growth in global wealth went to the top 1%, whereas the bottom 50% saw no increase at all. The SDG-10 calls for reducing inequalities in income as well as those based on age, sex, disability, race, ethnicity, religion, or other status within a country. Large inequalities in child health exist between, as well as within, countries. For example, in Bolivia and Peru, the richest one-fifth of the population has almost universal access to a skilled attendant at birth, compared with only 10% to 15% among the poorest one-fifth. Women in poor rural households accounted for two-thirds of unattended births.

Although the United States spends more on health than any other country ($10,348 per capita), it ranks lower than other highly developed nations with respect to its under-5 mortality rate (7 deaths per 1,000 live births), which is greater than rates in most of Europe. Additionally, the United States lags behind other comparable countries with worse life expectancy and higher rates of disease burden as calculated in disability-adjusted life-years. Significant health inequities are also apparent within the United States. Black children age 1 to 4 years have the highest death rates (38.8 per 100,000), followed by Native American children (30.5 per 100,000); Asian/Pacific Islander children have the lowest death rates (16.5 per 100,000). Much of the differences in health outcome are the result of disparities in nonmedical social determinants, such as income and education. Compared with other Western countries, however, the United States spends disproportionately more on health care than on social services that could indirectly improve health outcomes.

To attain the SDGs of reducing child mortality, targeted interventions that focus on the poorest populations are needed that could close gaps in intranational health disparities. It has been projected that policy interventions aimed at reducing country-level inequities would have a major effect on the under-5 mortality rate. Worldwide, had the child mortality rates of all countries been reduced to that with the lowest rate (2.1 deaths per 1,000 live births), a total of 5.1 million deaths of under-5 children could have been prevented in the year 2017 alone, which would represent a 95% reduction of child deaths.

The Health and Medicine division of the National Academies (formerly the Institute of Medicine) definition of *global health* (GH) encompasses "health problems, issues, and concerns that transcend national boundaries, and may best be addressed by cooperative actions...." For the World Health Organization, GH involves health problems that affect global politics and economies and arise from disparities in sociopolitical and economic status. Inequalities in health within and between countries arise from inequalities within and between societies. Consequently, the emerging field of GH intersects medical and social science disciplines such as demographics, economics, epidemiology, political economy, and sociology.

Integrating Global Health Into Pediatric Careers

Children constitute the most vulnerable group in any society, and the strongest medical advocate for the health of children is the pediatrician. Consequently, pediatricians have been leaders in addressing global and local health disparities, and their collective voice has been powerful. Global health work varies widely in scope and extent. The duration of GH activities ranges from single short-term medical missions to long-term postings in resource-limited settings. Involvement in GH encompasses the direct provision of clinical services, technical assistance for program development, research, education and training of health workers, and governmental advocacy for policy changes. The goals of GH activities range from forging novel directions in areas of basic science and epidemiologic, clinical, and operations research to addressing the needs of the world's poorest communities. Ideally, GH experiences should be transformative for the health professionals who engage in these experiences and for the poor communities of the world that they serve.

By committing to a single international site (eg, hospital, rural clinic, community) and working with a partner based at that site, the pediatrician can engage in a longitudinal supportive relationship that is sustainable and effective. Pediatricians can also make a sustainable impression by empowering in-country partners through training of trainers, such as community health workers, supervisors, and clinicians responsible for health professional trainees.

Pediatricians may engage in GH activities in multiple domains, including patient care, teaching and training, research, and advocacy. Pediatricians have also played an important role in responding to humanitarian emergencies in the United States as well as in other countries, such as in the aftermath of devastating earthquakes and other natural disasters. Additionally, pediatricians with skills in research and evaluation may contribute to GH through clinical research and program evaluations.

Many GH opportunities do not require an overseas trip. Although vulnerable populations and health inequities certainly exist in low-income countries, significant inequities abound in the United States. Among developed countries, those with the highest health status have the lowest levels of health inequality. The United States ranks at the bottom of this list, with 1 of the poorest health rankings and the highest inequalities in health. Opportunities to engage in local GH work are plentiful and include supporting the care and resettlement of local refugee and immigrant families, supporting international adoptees, serving migrant farmworkers, and supporting Native American health issues.

The pediatrician may also work locally for GH by advocating for equity of health care at all levels domestically and globally, working in the home office of a US-based GH organization, and providing expertise to support international organizations dedicated to helping vulnerable children. Finally, pediatricians can make a significant impact in GH by lobbying the US government for more international relief funding or supporting corporations with ethical international trade practices.

Beyond the Hospitals: Global Health, Community Health, and Advocacy

Increasing numbers of medical students and residents in the United States seek training opportunities in developing countries, and most of these trips are spent in a foreign hospital on a pediatric

ward providing direct clinical care. In addition to observing and managing tropical diseases and more severe forms of commonly encountered pediatric conditions, visiting physicians and students learn and experience common themes in these low-resource settings: underpaid and under-trained health workers, hospital administration untrained in health management, dilapidated facilities, basic medicine shortage, lack of tools in testing and imaging, and higher mortality rates. Because the needs at such hospitals and clinics are glaring, the physician instinctively seeks to fill the gaps with what defines quality health care in the United States—more medicines, equipment, clinical staffing (in the form of visiting physicians), and perhaps training. However, the long-term effect of a brief visit, even repeated visits, may be further improved through efforts to prevent disease using public health approaches and focusing on communities.

With additional training in areas such as public and community health or health service management, the pediatrician may act as an "agent of change" by undertaking systems-based quality improvement approaches, public health measures, and community-based strategies to bring about lasting positive effects on child health.

Box 9.2 lists some key categories of GH organizations. In collaboration with community groups, the clinician or student can effectively empower community health workers and work within local community-based nongovernmental organizations (NGOs) to contribute to lasting and contextually appropriate change.

Getting a sense of how most of the world lives is a tremendous gift, honor, and burden that accompanies these experiences. Continuing to advocate for children living in poverty throughout the world after returning from a short-term medical experience is a great way to enact one's ongoing responsibility. Additionally, although perhaps less glamorous than traveling overseas, working within the US health care and political system to promote awareness for change has the potential to catalyze lasting and significant improvements in child health. Similarly, through work to empower local refugee communities in the United States or to advocate for more equitable access to health care for vulnerable immigrant children, pediatricians can make a significant and lasting difference in the efforts to close the gap in health disparities.

Ethical Issues in Global Health

The traditional model for medical experiences for US-based physicians presumes that individuals in the United States possess the knowledge, skills, and resources to improve the conditions of people living in developing countries. Most students and physicians who have participated in such an experience, however, report that they themselves derive the greatest benefit from such experiences.

Although the desire to improve the conditions of children by providing clinical care is well-intentioned and altruistic, the potential exists for short- and long-term harm. In the short term, caring for children in such settings with conditions that are unfamiliar to visiting students or physicians and out of the scope of their training can result in errors in diagnosis and management. Often, students have less supervision of their clinical work in these settings, which

Box 9.2. Examples of Global Health Organizations

International Health or Multilateral Organizations
- World Health Organization (WHO)
- United Nations Children's Fund (UNICEF)

Bilateral Government Organizations
- US Agency for International Development (USAID)
- Centers for Disease Control and Prevention (CDC)
- Peace Corps

International Donor Foundations
- Bill & Melinda Gates Foundation
- Wellcome Trust
- Children's Investment Fund Foundation (CIFF)

US-Based Nongovernmental Organizations
- Partners In Health
- Global Health Council
- Save the Children

International Nongovernmental Organizations

Specialized services or training
- Short-term service/training trips (eg, cleft palate repairs)

Emergency relief and rehabilitation
- Doctors Without Borders (Médecins Sans Frontières)
- International Committee of the Red Cross
- CARE International
- International Rescue Committee (IRC)

Consultant Organizations: For-profit and Not-for-profit

Global health consultant organizations may take government contracts to provide international support
- Seed Global Health (formerly Global Health Service Partnership)
- FHI 360 (formerly Family Health International)
- John Snow, Inc. (JSI)

Faith-Based Organizations
- World Vision
- Aga Khan Foundation
- American Friends Service Committee

Academic Institutions

An increasing number of academic institutions are developing global health programs in partnership with international groups, overseas academic institutions, or ministries of health
- Consortium of Universities for Global Health (CUGH)

Local and Domestic
- Global health advocacy organizations
- Refugee resettlement agencies
- Native American health services

Resources
- American Academy of Pediatrics Section on International Child Health (AAP SOICH)
- Academic Pediatrics Association Global Health Special Interest Group
- Physicians for Social Responsibility (PSR)

Table 9.1. Preparation for Working in Resource-Limited Settings: Themes, Subcategories, and Examples

Category Themes	*Subcategories*	*Example of Recommendations for Best Practices*
Logistics and safety	Personal health Safety Travel logistics Medical licensure Malpractice insurance	Create strategies for risk reduction, including for transportation, environment, food, risk-taking behaviors, and recreational activities, and emphasize that local laws (eg, seat belts, restricted areas) apply to all visitors
Knowledge and skills	Medical knowledge Health systems knowledge Procedural and practical skills (if applicable)	Familiarize oneself with local disease patterns, reference materials, on-site formularies, and clinical practice guidelines, including resources available through the World Health Organization
Attitudes and behaviors	Personal motivations Learner humility Cultural humility Understanding of culture shock and reentry shock Professionalism and behavior	Recognize that behaviors, skills, and competencies of local providers are culturally based and resource-dependent, and avoid comparison with home institutions, superior or judgmental attitudes, and denunciations of differences in clinical care
Local resources	Clinical resources Human resources Needs and assets	Familiarize oneself with the host site formulary, laboratory supplies, radiology capabilities, medical technology, medical transportation services, patient costs, and patient payment models before departure to best inform adaptations in diagnostic evaluations and management
People	History, politics, and economics Culture Religion Local health beliefs Language	Arrange plans for interpreter services during the visit, if necessary, and recognize the burdens imposed on local health professionals when assisting with interpretation
Ethics	Donations Research and projects Patient privacy Patient care with resource limitations Scope of practice Supervision Sustainability Effect on hosts	Follow host institution guidelines and accepted international guidelines about the donations of medications, technology, and supplies
Communication	Predeparture, on-site, and post-return communications	Schedule meeting with returning traveler to assess wellness, provide an opportunity for debriefing of the experience, obtain input on the program or partnership strengths and weaknesses, and determine the effect of the experience on clinical practice and career plans
Partnerships	Choosing opportunities Predeparture selection processes Clear expectations Evaluation	Provide transparent goals and objectives for both visitors and the sending institutions and ensure that the host institution has an opportunity to review them and modify them if necessary

Adapted with permission from St Clair NE, Pitt MB, Bakeera-Kitaka S, et al; Global Health Task Force of the American Board of Pediatrics. Global health: preparation for working in resource-limited settings. *Pediatrics*. 2017;140(5):e20163783.

can result in harm to patients and students' growth as physicians. In the long term, provision of clinical care by visiting students or physicians can undermine the existing health system infrastructure.

As the number of medical students, trainees, and physicians from the United States who visit developing countries for short-term training experiences continues to grow, concern for medical tourism and the long-term effect of these training experiences on the under-resourced hosts is rising. As indicated in Table 9.1, key factors for ensuring effective, sustainable, and ethical international collaborations include forethought, planning, and long-term partnership. Key guiding principles of effective and sustainable partnerships include equity, inclusivity, sustainability, mutual benefit, prevention of adverse effect, social justice, and humility. Although most partnerships in GH involve trainees and practitioners from a higher-income country visiting a facility in a low-income country, everyone may derive greater benefit from reciprocal exchanges; such bidirectional exchanges impart true parity within partnerships.

Proper predeparture preparation and education for any overseas medical experience is a critical first step and entails orientation about the country and its sociopolitical context and public health priorities. Knowledge of the key medical problems facing the communities as well as international and local treatment guidelines and strategies to deliver care within the confines of existing local resources are also important. Critical key minimal standards for preparation are described in Table 9.1.

The fundamentals for the creation of a meaningful international partnership with a community involve multiple steps. The first step is the development of a mission or an identified shared purpose with partners before visiting a new international site. Second, it is critical to establish a collaboration with a local agency, such as an NGO or a governmental agency, to promote sustainability and enhance effectiveness of the care delivered. A third important step for long-term effect and partnership is to ensure that the education of community members, other physicians, and trainees is a part of the mission and that appropriate educational experiences are structured into the trip and planning. Closely related to this is the appreciation of the reciprocal nature of any education: The visiting physician is in a position to learn just as much if not more than the local health workers about working in the local setting.

A fourth fundamental step for meaningful partnerships involves ensuring that service is truly being provided to the community by learning about the health priorities of the community from the NGO or other local agency. It is also important to encourage teamwork by working with appropriate supervision, including physicians from the host country. Effective international collaboration also requires sensitivity to the costs and burden that a visitor has on the host. Finally, assurance of partnership effectiveness requires building an evaluation process early on that incorporates the perspectives of all involved, including local officials, health professionals, and community members. This includes assessment of whether educational objectives are being met for all stakeholders, including the host site.

CASE RESOLUTION

You learn about a US-based NGO with a long history of partnership and work in the earthquake-stricken country. You research that NGO further and learn that it is a reputable group with long-term interests in the country. You speak to friends who have recently visited the country and learn more about what skills and resources are needed. You arrange to join a team of experienced health workers from the NGO by taking time from work and garnering support from your family to manage in your absence. You undergo an in-depth orientation of the site, people, sociopolitical situation, team roles, and expected activities through a series of discussions with all participants.

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CHAPTER 10

Child Advocacy

Marni E. Shear, DO, FAAP, and Grant P. Christman, MD, FAAP

CASE STUDY

A 7-year-old boy is brought to the emergency department by his mother with acute onset of respiratory distress. He awoke from sleep with a coughing fit and has not been able to catch his breath since. His mother explains that her son was admitted to the hospital with similar symptoms 1 month previously and was diagnosed with asthma at that time. Although the boy was prescribed 2 inhalers during his hospital admission, his mother reports she no longer has these because her son has not needed them. She also explains that her child has a daily nighttime cough and frequent coughing with exercise. After administration of an oral steroid load and 3 doses of ipratropium bromide and albuterol sulfate, the child's breathing improves somewhat. He is admitted to the inpatient pediatric service for ongoing asthma management and care.

Questions

1. What does it mean to be a child advocate?
2. Aside from caring for individual patients, how can pediatricians promote the well-being of their communities?
3. What is the role of the pediatrician in child advocacy?
4. What are the levels of advocacy?
5. How does the pediatrician implement advocacy?

An *advocate* is someone who speaks on behalf of a person or cause. No group in our society has a greater need for advocates than children. Children are ill-equipped to face the many threats to their health; they cannot obtain their own health insurance, access available social services, or get themselves to the doctor when sick. Additionally, children have limited influence compared with adults in our society. They cannot vote, donate money to political campaigns, or speak publicly to advance their interests. The word "advocate" is derived from a Latin root meaning "one who has been called to another's aid." From the beginnings of pediatrics as an independent branch of medicine, pediatricians have answered this call to advocate for the health and well-being of children.

Abraham Jacobi, MD, who is often referred to as the father of pediatrics in the United States, spent his career in the late 1800s and early 1900s advocating for children through legislation in New York and the District of Columbia. He addressed issues such as breastfeeding, food and water contamination, and conditions in foundling homes. He urged physicians to be involved in public life and policy making, and he was the founder and first president of the American Medical Association (AMA) Section on Diseases of Children. Another founder of pediatrics in the United States, Job Lewis Smith, MD, recognized the need for a clean water supply and decent housing to decrease the high infant mortality rate of his time. He worked through public advocacy to improve living conditions for all children, and he was the founder of the American Pediatric Society, which was the first pediatric medical society.

In 1921, the US Congress passed the Sheppard-Towner Act, the first major federal program to specifically address maternal and child health. It provided matching funds to states for services for pregnant women and new mothers. The AMA, which was concerned about government interference in the practice of medicine, condemned the act, whereas the AMA's own Section on Diseases of Children supported it. Conflict related to the Sheppard-Towner Act ultimately resulted in the pediatric group leaving the AMA and founding the American Academy of Pediatrics in 1930. The American Academy of Pediatrics has been advocating for children ever since.

The New Morbidity

Advocacy remains important because the "new" morbidities in pediatric medicine, some of which are new and others of which are only newly recognized, are related to social and economic forces. Child health outcomes improved dramatically in the 1900s with the development of vaccines, antibiotics, and new and improved surgical care to manage the classic morbidities of infectious disease, infant mortality, poor nutrition, epidemics, overcrowding, and chronic disease. New morbidities that were recognized in the 1960s to 1980s, as described by Robert Haggerty, MD, included family dysfunction, learning disabilities, emotional disorders, and educational problems. In the 1980s to early 2000s, Judith Palfrey, MD, documented new challenges for pediatricians: social disarray, political ennui, the sequelae of high-tech care, and new epidemics of violence, AIDS, cocaine, and homelessness. The newest morbidities of the 21st century include the increased prevalence of childhood obesity, bullying, significant health disparities among cultural and socioeconomic groups, and the growing population of children with special health care needs. Mounting evidence, such as provided by the Adverse Childhood Experiences Study conducted from 1995

through 1997 by the Centers for Disease Control and Prevention and Kaiser Permanente, has demonstrated the critical need to identify and mitigate sources of toxic stress, which can pose a long-term threat to the developing brain.

Although improvement has occurred in recent years, many children in the United States continue to face challenges in obtaining access to quality health care. The 2015 National Health Interview Survey found that children without health insurance were less likely to have a usual source of care and were more likely to postpone seeking care than children with health insurance (Figure 10.1). In the past several decades, government programs such as Medicaid and the Children's Health Insurance Program have expanded the availability of health care coverage to children of limited financial means. The passage of the Patient Protection and Affordable Care Act in 2010 (PPACA) resulted in significant increases in access to health care for many pediatric populations. The number of children younger than 18 years with no health insurance coverage decreased from 6.6 million in 2012 to 3.9 million in 2016; however, 1 in every 20 children remained uninsured as of 2016. Among children in poverty, the uninsured rate was 7%, compared with a rate of 5% for children not in poverty. Racial and ethnic minorities were also more likely to be uninsured, with Hispanic children having the highest rate at 7.9%. As of 2016, approximately 40% of all children were receiving coverage from public insurance programs, an increase from 2010. With ongoing legislative efforts to either repeal PPACA or reduce benefits, the future of access to health care for children remains in jeopardy.

These significant issues affecting child health cannot be adequately addressed on an individual basis. Advocacy on a community or national scale is required to improve child health outcomes and quality of life for children.

Levels of Advocacy

Every pediatrician serves as a child advocate on a daily basis. With every patient encounter, the pediatrician advocates for care in the best interest of the patient. This first level of advocacy includes treating the individual's immediate medical needs, that is, performing screening tests, providing anticipatory guidance, and coordinating referrals as necessary. In addition to providing direct medical care, the pediatrician may advance the welfare of the child by, for example, writing letters to help a patient obtain social services, or visiting a patient's school for a meeting on creating or reviewing an Individualized Education Program.

The second level of advocacy is community advocacy. The AAP policy statement "The Pediatrician's Role in Community Pediatrics," describes "community pediatrics" as a perspective that broadens the perspective from a focus on the individual patient to all the children in the community; a recognition that family, education, society, culture, spirituality, economy, environment, and politics all affect the health of children; a synthesis of clinical practice and public health principles directed to providing health care to a child and promoting the health of all children; a commitment to collaborate with the community to optimize health care for all children, especially disadvantaged children; and recognition that community pediatrics is integral to the role of the pediatrician. The pediatrician has a responsibility to improve conditions in the community to benefit patient health. To do this, they must be familiar with the services that are available for children. They can develop relationships with child care centers, schools, community coalitions, city governments, and local organizations to advocate for the best interests of children. Examples of potential involvement in the community include serving as a board

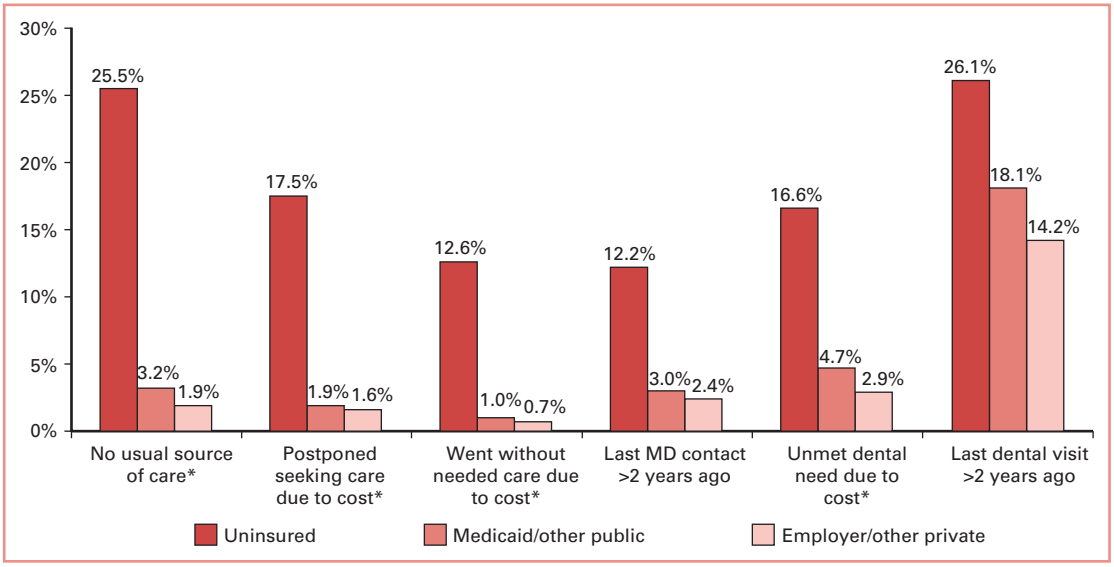

Figure 10.1. Children's access to care by health insurance status in the United States in 2014.

* In past 12 months. Questions about dental care were analyzed for children age 2–17 years. All other questions were analyzed for all children younger than age 18 years. MD contact includes other health professionals. Respondents who said usual source of care was the emergency department were included among those not having a usual source of care. All differences between the uninsured and the 2 insurance groups are statistically significant ($P < 0.05$). Adapted with permission from Kaiser Family Foundation analysis of 2015 National Health Insurance Survey (NHIS) data. https://www.kff.org/wp-content/uploads/2015/11/children_s-access-to-care-by-health-insurance-status.png

member of a community organization, developing health agendas, working with an existing organization to design and fund a community service project, and being a source of information for the community on child health issues.

On the state level (the third level), pediatricians can work to improve health care resources or develop policies to help and protect children. Opportunities for involvement include working on legislation, budgets, regulations, and initiatives or working with the executive branch of local and state government. The fourth level of advocacy is the federal level; at this level, pediatricians can educate their senators and congresspersons on child health issues. Pediatricians may also testify before a congressional subcommittee. The fifth and final level of advocacy is the international level. For example, a pediatrician may choose to work with the World Health Organization to improve immunizations for all children worldwide. Global child health is currently a focus of many advocacy training programs.

At the local, state, and national levels, voting remains a powerful tool for the pediatrician to advocate for child health and welfare. In addition to voting themselves, pediatricians can encourage their patients to register to vote when they reach the age of eligibility.

Becoming a Child Advocate

To become an effective child advocate, the pediatrician must first identify an issue that he or she wants to change or set a goal to improve the lives of children. The more specific the issue or goal, the easier it is to develop a solution. Ideas often arise from clinical practice, in which repeatedly engaging in individual advocacy efforts on behalf of patients with the same problems suggests the need for a larger solution. The first step in taking action is to obtain background information about the problem and collect objective data that support the need for change, then define the nature of the problem and the affected population in clear and precise terms. Child health data from public agencies and private organizations are increasingly accessible via the internet.

Community Projects

Alternatively, a pediatrician may find that an issue is best addressed through a community advocacy project. In developing such a project, the pediatrician's relationship with the community is of utmost importance, and the pediatrician should endeavor to become familiar with the community as a whole. Community exploration, which may be as simple as walking or driving through a community and observing, can reveal areas of need, such as dilapidated housing or unsafe streets. Equally important is the discovery of the community's assets, including institutions such as places of worship, schools, and banks, which strengthen a community and are potential sources of support for and counsel about the project. Pediatricians should view themselves as members of the community, acting from within and in collaboration with the community, rather than as outsiders bringing about change externally.

The next step is to develop an intervention. After the possible solutions are considered, the pediatrician should collaborate with community stakeholders to develop and implement the most practical solution. Having credibility in the community makes the task of collaboration much easier. Collaboration requires the ability to compromise and be flexible in developing and implementing plans. Larger projects may require funding, and grants may be sought from advocacy organizations, foundations, the government, or even local businesses. Data should be collected during the intervention to monitor the success of the project and then shared publicly with members of the community as well as with leaders who can shape policy (eg, legislators). If the project is successful, its methods may be adopted by child advocates in other communities.

Legislative Advocacy

Although involvement in the legislative process is initially daunting for the physician without political expertise, often it is the only means by which to effect a desired change for children's health. Information about the content and progress of existing bills is readily available online, and legislators can be contacted by letter, email, or telephone to offer a position. It is helpful to become familiar with the process by which a bill becomes a law, both at the state and the federal level; the identities of the important players change as a bill progresses through the various subcommittees and committees and ultimately proceeds to a floor vote.

Pediatricians may also arrange to meet with a legislator or staff member at a district or capital office to discuss their position personally. In the dual role of scientist and healer, the pediatrician is in a unique position to inspire both the heart and the mind. It is important to state the problem clearly and explain why a new law is the solution, present well-researched facts that support the position, and use clear language, avoiding medical jargon whenever possible. The pediatrician should minimize the appearance of self-interest by focusing on how the proposal will help children, rather than how it will benefit the profession. It may also help to connect with the legislator by sharing a story about a patient encountered in practice who has been affected by the problem, especially if the patient is a constituent of the legislator (although the patient's identity must never be discussed without the patient's consent). Providing the legislator a concise fact sheet summarizing the position and the pertinent background information helps ensure that the position is not forgotten when the legislator is considering the issue at a later date.

The pediatrician should be prepared to encounter opposition from some legislators and avoid responding with angry statements that would be alienating. Effective advocacy requires building relationships with legislators over the long-term, and a legislator who opposes a position 1 year may be a potential supporter the next year, when the political climate changes, or may be a potential ally on another important issue. Among the several other pitfalls to be avoided include making or agreeing with partisan statements or claiming to represent an organization (eg, AAP) or an institution (eg, a university) without authorization. When asked a question to which they pediatrician does not know the answer, it is best to avoid guessing and to instead offer to do further research and provide the requested information to the legislator at a later date.

When developing a new legislative proposal from scratch, it is necessary to remember that although the factors contributing to child health are numerous and complex, each legislative proposal must by nature be concrete and limited. It may be best to start small and work for incremental change. The first step is to identify a clear and, if possible, measurable, objective and define the target population. Other important information to know when drafting a proposal includes any potential funding sources (if applicable) and which government agencies might be involved in implementation or enforcement. The pediatrician should partner with 1 or more legislators early on, not only because a bill must be sponsored by a legislator to be considered for passage but because many of the finer points of the legislative process are outside the experience of the average pediatrician. Building a coalition of support within the community and involving important stakeholders such as politicians, business professionals, other health professionals, educators, and parents, will help the bill gain political support.

Opposition should be expected, and potential sources of opposition should be identified in advance. If opposition from a powerful interest group is anticipated, it may help to meet with a representative of that group to explain the proposal. Potential arguments might include ways in which the proposal is really in the group's best interest, the moral imperative to help children, or the potential for negative publicity by opposing an initiative to benefit children. Compromising on aspects of the proposal should be considered when doing so might turn a detractor into an ally. When facing intractable opposition from powerful interests, pediatricians and supporters should strive to recruit even stronger allies into their coalition.

The process of turning a policy idea into legislation may be lengthy. It may be necessary to reintroduce a bill repeatedly over several years before achieving passage. After a bill becomes a law, advocates must continue working to ensure that necessary funds are allocated during the budgeting process, that public agencies implement the law as intended, and that the law is reauthorized when necessary. Physicians who are recognized as experts in child health policy will be called on to testify before committees in Congress or the state legislature on policy issues affecting children.

Media Advocacy

The media, including newspapers, magazines, radio, television, and the internet, are extremely influential. News stories about child health and welfare may not always be written from a child-friendly point of view. The pediatrician plays an important role in providing the media with better information and a different angle on a story. For instance, a pediatrician reading a newspaper story about a child who exhibited signs of autism shortly after his 1-year-old physical examination might write a letter to the editor discussing the lack of scientific evidence for a connection between vaccinations and autism. Over time, a pediatrician can develop relationships with local journalists, who can then turn to the pediatrician for information when covering child health stories.

A directed media campaign may also be a key element in an advocacy project. At the community level, the media can help educate the public about child health practices, notify the public of events, and bring out potential allies and coalition members. When advocating for legislation, the pediatrician can use the media to reach legislators directly and, equally important, reach thousands of the legislators' constituents simultaneously, who may in turn help pressure their legislators for change. In such situations, it is essential to plan a media strategy in advance by determining the most important target audience, selecting the appropriate types of media to approach, crafting a message appropriate to those media, and preparing thoughtfully for encounters with journalists.

Getting Connected

The AAP is a vital resource for pediatricians interested in child advocacy, with opportunities for involvement offered through the AAP Department of Federal Affairs, as well as the various state chapters advocating at the state and local levels. The AAP has also established a network of pediatricians who advocate through social media, using Twitter as a communication platform on which Tweetiatricians can initiate and facilitate conversations on various topics related to child health. A social media toolkit is available through the AAP to help pediatricians choose the best platform for their specific outreach goals. In an effort to promote understanding of the effect of poverty and social determinants on child health, the Academic Pediatric Association has developed a robust curriculum to help deepen understanding of income disparities, social determinants of health, health care delivery systems in the United States, and opportunities for legislative advocacy. Other national organizations with which pediatricians may become involved and that provide advocacy toolkits include Docs For Tots (http://docsfortots.org), Children's Defense Fund (www.childrensdefense.org), Children Now (www.childrennow.org), the National Center for Children in Poverty (www.nccp.org), and the Child Welfare League of America (www.cwla.org).

Improving the health of all children through advocacy is considered to be the responsibility of pediatricians and can be a tremendously rewarding part of pediatric practice.

CASE RESOLUTION

Managing this child's asthma is only the first aspect of thorough pediatric care. For the pediatrician to advocate for this patient and prevent a third admission for a subsequent and potentially worse asthma exacerbation, it is necessary to obtain essential information, such as the patient's social history and the environment in which he lives. A thorough social history is obtained and reveals that the child lives with his mother and grandmother. The mother recently lost her job, and she and her son moved into a 1-bedroom apartment with the child's grandmother. The apartment has old carpeting, and the mother expresses concern about mold on the walls. The child's grandmother smokes cigarettes, but she avoids smoking in the apartment when the child is home. The patient and his family are counseled about his diagnosis of asthma and potential asthma triggers. The grandmother expresses interest in smoking cessation, and resources are provided. The family receives an asthma action plan and education on the use of a metered dose inhaler with a spacer, and the pediatrician uses the teach-back method to ensure understanding of the plan of care at discharge. The pediatrician becomes concerned about the high prevalence of asthma in the community and explores coalitions in the area that recognize similar concerns. He becomes a member of the coalition steering committee and works with the local health department and other community stakeholders to develop a home-based intervention program in which community health workers provide families with in-home environmental assessments, education, and support. As a result of the coalition's efforts, the child's home is 1 of many apartment complexes in the area assessed by the local housing authority, and resultant action is taken to bring the property up to health and safety standards.

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PART 2

Principles of Health Care and Pediatric Management

CHAPTER 11

Health Systems Science

Stephanie R. Starr, MD, FAAP

CASE STUDY

You are seeing Sara, a 14-year-old girl with multiple health issues (ie, asthma, obesity, acanthosis nigricans, mood disorder, attention-deficit/hyperactivity disorder, posttraumatic stress disorder) for a follow-up visit for a recent concussion. You know her family (ie, mother and sister) well. She has frequent emergency department visits for abdominal pain, asthma exacerbations, and headaches. You frequently lack sufficient time during visits to address all her concerns and the health issues you want to discuss. The mother has been unemployed for several years. Your team has had some challenges reaching her family when visits are missed. You sincerely want to help Sara and her mother meet their health goals for Sara but feel that providing the best care during office visits is not making a significant difference in her health.

At today's visit, the mother asks for head imaging because she is concerned about Sara's ongoing dizziness and headaches; however, her neurologic examination is normal and she does not have any "red flag" symptoms or signs that warrant head imaging. You want to be patient- and family-centered, but you are concerned about the risks and costs of unnecessary testing.

Questions

1. How might you approach the conversation with Sara and her mother in response to their request for imaging?
2. How are evidence-based medicine, "less is more" conversations, and shared decision making related to high-value care?
3. What other health systems science-related issues do you recognize in Sara's story, and what systems strategies might be considered to improve her health and experience of care?
4. What microsystem-level actions could you and your care team use to improve the health care and outcomes of similar patients in your pediatric practice?
5. What macrosystem-level actions could you and your colleagues take to improve the health care and outcomes of similar children in your health system or community?

Introduction

Rapid Evolution of US Health Care and Persistence of Significant Gaps in Health

For decades, primary care pediatricians have focused on the individual needs of infants, children, adolescents, young adults, and their families, and have made every effort to provide the highest quality care to their patients. The components of primary care and the patient-centered medical home are ideally combined to optimize the care of children using a holistic approach (see Chapter 1). The role of the primary care pediatrician is changing from managing acute illness to preventing illness to diagnosing and treating new morbidities, such as mental health disorders, neurodevelopmental disabilities, chronic disease, and other disorders that often stem from socioeconomic determinants of health, including poverty, family dysfunction, abuse, and other adverse childhood experiences. Although advocacy (see Chapter 10), culturally competent care (see Chapters 8 and 57), and global child health (see Chapter 9) have long been emphasized in caring for pediatric patients, these new morbidities and other changes in the lives of patients and their families require an explicit focus on new topics. Social determinants of health are estimated to contribute more toward health outcomes than health behaviors, care via the health care system, or genetics. Advances in shared decision making and conversations with patients and families on choosing tests and treatments that are high value to patients, families, clinicians, and the system require new clinical skills not traditionally taught in caring for individual patients.

As children, their families, and their health issues have changed, so have pediatric practices and the broader US health care system. In 2007, the Institute for Healthcare Improvement proposed Triple Aim as the ultimate goal of health care, that is, optimal health of the population and best experience of care at the lowest cost. Health care stakeholders (ie, patients, families, payors, insurers, health professionals, health care systems, society) more commonly frame this as value, that is, the quality of care (ie, care that is safe, timely, effective, efficient, equitable, and patient-centered) divided by the cost of care over time. Health care spending does not correlate to health outcomes, and health care costs are the largest contributor to personal US bankruptcies. Substantial gaps in health care access, equity, affordability, safety, effectiveness, and efficiency persist despite significant advances in biomedical science. Primary care pediatricians and other health professionals are advancing child

health via health care improvement (ie, quality improvement [QI], patient safety [see Chapter 21]) initiatives locally, regionally, and nationally. Doing so requires the ability to see levels of the health care system beyond the individual patient alone and to espouse the professional responsibility to care for the system in addition to caring for individual patients. In current practice, some health professionals have added a fourth aim: wellness of the health professionals and others on the care team.

Many interactions and systems issues that affect health care and health underlie every physician-patient interaction (Figure 11.1). This complex health care system is rapidly changing, including but not limited to payment models and insurance reform, new care delivery models, population health strategies, and emerging technology. Medicine and health care have become a team sport, with less focus on the physician-patient interaction alone and increased incorporation of interprofessional health teams into the patient-centered medical home model. Although pediatric health issues have changed significantly and the health care system is constantly evolving, little has changed in the training of the primary care pediatric workforce. The American Academy of Pediatrics (AAP) "Agenda for Children 2017-2018" includes topics not traditionally learned in medical school or residency, including access, finance, and social determinants of health. Practicing pediatric health professionals enter the profession with a steadfast commitment to improving the health of children, and many identify additional learning that would help them practice in this rapidly evolving health care system.

Medical Education and the Needs of Society

Medical education has an obligation to improve quality of life, reduce the burden of disease, and help advance the Triple Aim to fulfill its contract with society. Despite gaps in health care quality and rising costs of care, little has changed in physician education since Abraham Flexner proposed reform in 1910. Accreditation and certification bodies have added requirements in some areas, such as the Accreditation Council for Graduate Medical Education Systems-Based Practice and Practice-Based Learning and Improvement competencies in residency and fellowship, but many changes are incremental and gaps persist. Because medical costs are the most common reason for personal bankruptcy filings in the United States and because of the desire to first do no financial harm, some health professionals have advocated for high-value care as the seventh competency required for graduate medical education.

Traditional physician training in basic and clinical science alone does not meet the current health needs. Many practicing health professionals identify additional learning that would help them practice in the rapidly evolving system and achieve the Triple Aim. To help medical education evolve to match the pace of change in practice, and in recognition that rigorous basic and clinical science training is insufficient to meet the Triple Aim, many medical educators are advocating for training physicians in a "third" science: health systems science (HSS; Figure 11.2).

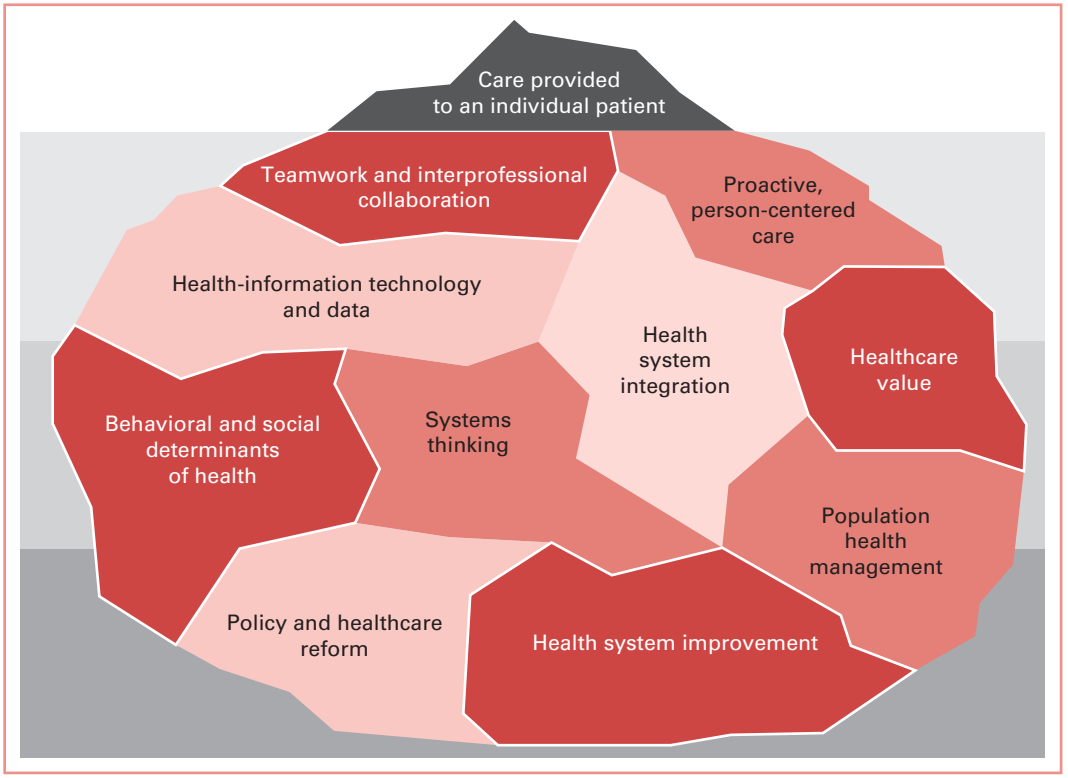

Figure 11.1. The "iceberg" of health care concepts affecting health.

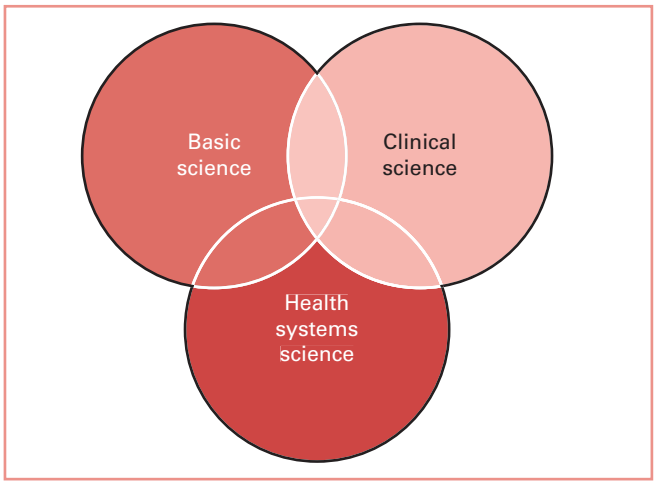

Figure 11.2. The 3-pillar model of medical education.

Health Systems Science in Medical Education

Health Systems Science Education: Definition, Framework, and Relevance to Primary Care Pediatricians

In 2017, experts from 11 medical schools published a curricular framework for HSS education to help address health and health care gaps. The curricular framework was proposed based on existing or planned systems-related curricula at their schools (Figure 11.3). *Health systems science* in medical education is defined as the principles, methods, and practice of improving quality, outcomes, and costs of health care delivery for patients and populations with systems of medical care. Stated another way, HSS can also be defined as the concepts and skills needed by health professionals to ensure that the basic and clinical sciences and the good intentions of health professionals have maximal effect on the Triple Aim.

The core content domains within HSS were described as health care structures and processes; health care policy, economics, and management; clinical informatics and health information technology; population and public health; value-based care, and health system improvement. Content areas (ie, cross-cutting domains) traditionally included in many schools but re-envisioned within HSS included scholarship; leadership and change agency; professionalism and ethics; teamwork and interprofessional education; and evidence-based medicine and practice. Systems thinking was described as the linking domain for the HSS framework.

Some schools use terms similar to HSS, such as "science of health care delivery," "health care delivery science," and "foundations of health care delivery" (Figure 11.4). Many medical schools in the United States and elsewhere are incorporating HSS-related curricula, with variation in scope and depth. The nomenclature related to this third science and the evidence for best methods to teach and assess it will continue to evolve. The old mantra "we are training students

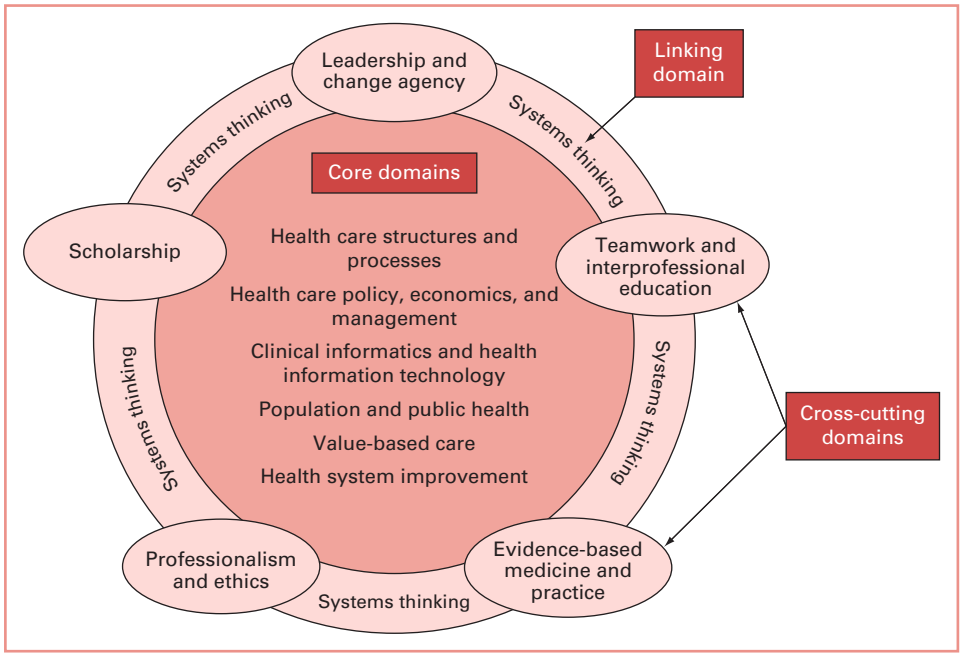

Figure 11.3. Core, cross-cutting, and linking domains for a health systems science (HSS) curricular framework. Core curricular domains are content areas that align directly with HSS. The cross-cutting domains are content areas that traditionally may have been included in undergraduate medical education curricula but that have a new context in the HSS. The 1 linking domain—systems thinking—unifies or links the core curricular or cross-cutting domains to other core curricular or cross-cutting domains (ie, internal linking, depicted in this figure) and to other areas of the curriculum, such as the basic and clinical sciences (ie, external linking, not depicted in this figure).

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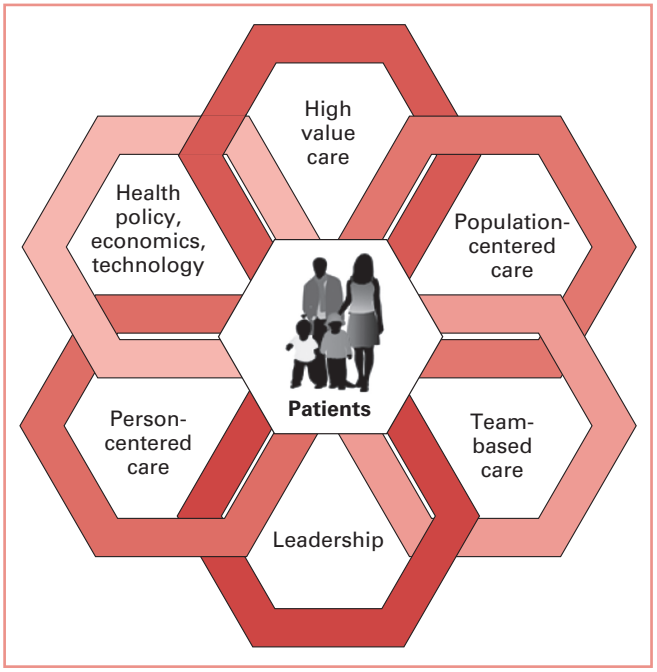

Figure 11.4. Health care curricular framework.
Reprinted with permission from Starr SR, Reed DA, Essary A, et al. Science of health care delivery as a first step to advance undergraduate medical education: a multi-institutional collaboration. *Healthc (Amst)*. 2017;5(3):98–104.

to care for tomorrow's patients" is no longer the ideal; schools are demonstrating that medical students can improve the care of today's patients as they learn about HSS.

Pediatricians in training and those in practice likely have significant variation in their understanding and practice of HSS-related concepts and skills based on their undergraduate medical education, graduate medical education, and/or their practice experiences. Although health professionals may have experience and expertise in some HSS-related areas, which for pediatricians includes a focus on advocacy and culturally competent care, they may not be able to easily explain relationships across HSS topics to team members and/or the students and residents they teach. Without a broad definition of the third science concepts that affect health and health care, pediatricians may miss opportunities to recognize and close gaps in care for children and their families. Pediatricians committed to caring for children can have great impact when they see their professional duty is both to doing their work (caring for individual patients) as they improve their work (caring for the health care system and for populations of patients). Envisioning HSS as a third science with a conceptual framework can foster systematic thinking and help pediatricians recognize the actions they can take (or "levers" they can pull) to meaningfully improve child and family health.

Systems Thinking: Components and Levels

Systems thinking is at the core of HSS. Pediatricians may recognize gaps in care that occur during office interactions with patients (eg, inability to identify a dentist who accepts the family's government health insurance) more easily than they can anticipate or see other gaps through the lens of the patients' and families' view as they experience care across a system. It can be difficult to really know what patients and families experience from the moment they call to try and schedule an office visit, to parking, to checking in to the front desk, to being led to a room by a nurse or other care team member, to being seen by the pediatrician, to going to the laboratory (on site or at a distance) for a blood test, to accessing test results and interpretation from the pediatrician.

Health professionals should ideally understand 3 essential concepts related to health care systems: systems thinking; the structures, processes, and outcomes comprising the building blocks of health care delivery; and effect on the patient of every level of the health care system.

Systems Thinking

The Waters Foundation has summarized 14 habits of systems thinkers that encourage health professionals to be flexible in their thinking, identify new insights, and appreciate other perspectives, including recognition that a system's structure generates its behavior. Stated another way, every process is perfectly designed to get the results it gets, so to get a different outcome, the structure and/or process must be changed as well. Systems thinkers can apply tools (many of which are used in QI training) to augment these 14 habits.

The Building Blocks of Health Care Delivery: Structures, Processes, and Outcomes

Avedis Donabedian, MD, MPH, considered by many to be the grandfather of US health care quality, explained the importance of improving health care quality by using structural, process, and outcomes measures. These measures provide a granular way of showing that health improvement efforts are "moving the needle" and having a positive effect (see Chapter 21). Examples of structure, process, and outcomes measures are given in Table 11.1.

Effect on Patients: Recognizing the Levels of the Health Care System

The effect—both positive and negative—on patients occurs at every level of the health care system, and clinicians must be able to recognize the levels of the health care system on behalf of patients and clinical team members. Patient- and family-centered pediatricians and their care teams consider the experience of care, disease, and treatment burden from the perspective of the patient and family. Pediatricians who think with a systems perspective are more likely to identify additional opportunities to improve care not only for their individual patients, but also for groups of similar patients. They can make or influence changes (ie, pull levers) not only at the patient-clinician level, but also at the microsystem, mesosystem, and macrosystem levels (Figure 11.5).

The *microsystem* is most familiar to pediatricians; it is the front-line clinical team that, in addition to physicians, may include nurses, nurse practitioners, clinical assistants, secretaries, and receptionists. Nurses on the team may have several specialized roles based on their scope of licensure, including clinic nurse, triage nurse,

Table 11.1. Examples of Measures to Assess the Quality of Pediatric Asthma Care

Structure Measures	*Process Measures*	*Intermediate Clinical Outcome Measures*	*Clinical Outcomes*[a]
Spirometry equipment and interpretation Asthma population database with support staff	Percentage of patients within the past 12 months with Updated asthma action plan ED visit or hospitalization Completed asthma control questionnaires Received influenza vaccine	Asthma control short-term Use of steroids in past year ED visits, hospitalizations in past year	Quality of life

Abbreviation: ED, emergency department.

[a] Most important to patients and families.

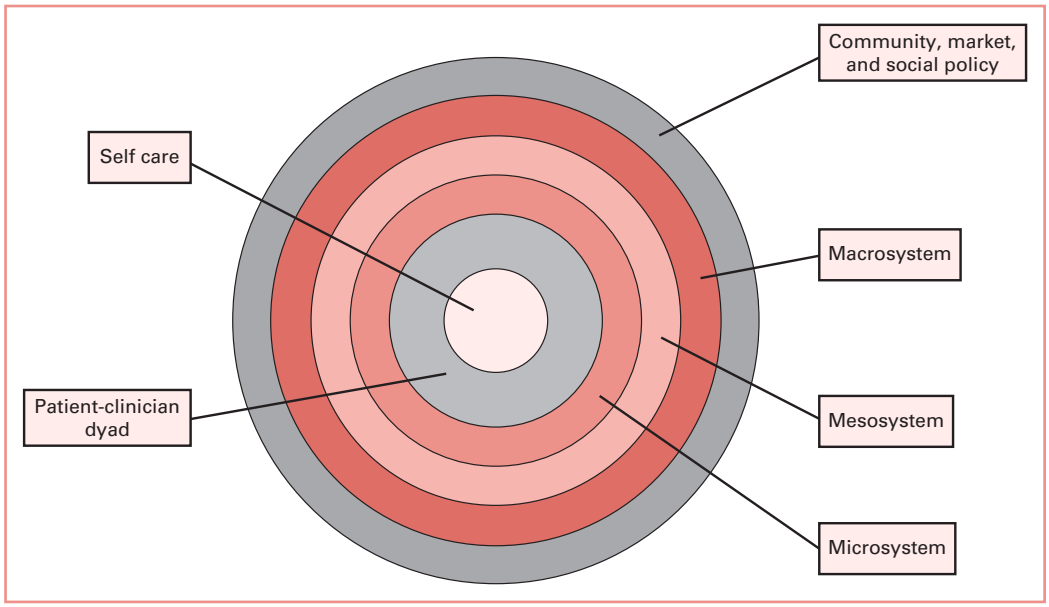

Figure 11.5. Levels of the health care system. Self care is care provided by patients and their families. Note that patients and/or families can obtain resources for their health directly from the community (outer circle). The microsystem is the front-line interprofessional clinical team with whom patients and/or families interface. In pediatric primary care, physicians, nurse practitioners, nurses, and secretaries are part of the primary care team/practice. The mesosystem comprises connected microsystems that patients and/or families traverse in their experience of care (eg, primary care team, inpatient care team, radiology team, pharmacy team, outpatient specialty care team, emergency department team). The macrosystem comprises mesosystems that patients and/or families traverse in their experience of care (eg, community health center, referral specialty health center, public health).

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and care manager (eg, for complex patients). Ideally, every team member has a role that enables that person to work at the peak of that individual's experience and licensure, and all perspectives are leveraged to recognize gaps in care and contribute to closing gaps (eg, via QI initiatives).

Mesosystems are collections of microsystems that a patient may move across during an episode of care. For example, a large multispecialty group practice at 1 clinic may have multiple pediatric, family medicine, and internal medicine teams (ie, microsystems) as well as other microsystems (eg, laboratory, radiology, and pharmacy teams). During a visit for possible pneumonia, a patient may move across 3 microsystems (ie, pediatric, radiology, and pharmacy teams) before leaving the clinic. Opportunities to improve the care of other patients like that one may occur at the microsystem level (eg, improving wait times) or may require a coordinated effort across 2 microsystems. Quality improvement and advocacy are levers that can be pulled to make or influence change at this level.

Similarly, *macrosystems* are collections of mesosystems across which a patient may move during an episode of care. An ill child seen in a primary care mesosystem who is transported to the emergency department mesosystem (with, for example, emergency

medicine microsystem, laboratory microsystem, radiology microsystem) and is later admitted to the hospital (with similar mesosystem members) encounters an entire macrosystem. The quality of care this child receives is dependent in part on the strengths or weaknesses not only of each team, but on how the teams communicate during handoffs and how everyone is able to envision the patient's journey from the start of his or her experience (ie, in the primary care office) to the end (ie, hospitalization and eventually, discharge home). To reiterate, both QI and advocacy can occur at the macrosystem level.

Applying Health Systems Science to the Components of Pediatrics

Primary Care

The components of primary care as described by Charney and Alpert in 1974 include first contact, longitudinal care, family orientation, and integration of comprehensive care (see Chapter 1). For all pediatricians working in the current US health care system, these components remain critical and relevant, but the pediatrician with a systems view will recognize the need for additional components and will understand that it is necessary to evaluate each component at multiple levels of the system to maximize the health of all children. Examples of each component at multiple levels of the health care system are described in Table 11.2. These examples are opportunities for pediatricians and colleagues in their clinical (ie, microsystem) teams to see opportunities to promote high-value care and improve child health and, in doing so, advance the Triple Aim.

Pre–First Contact

The process or steps that patients and families encounter before having their first contact (ie, office visit) was not conceptualized when medicine and care delivery outside of public health was purely transactional, an interaction between the patient and the physician (or in the inpatient setting, a patient and a hospital team). Variation in access to care based on health insurance, geography, transportation, and other barriers now affect how a patient interacts with primary pediatric teams in primary care medical homes. Pediatricians and pediatric medical homes seeking to improve child health care and health must conceptualize their role in ensuring the patients in their care have access to care when they need it and to preventive care to maintain their health.

For example, in 2015 the National Academies of Sciences, Engineering, and Medicine (NASEM) published a white paper titled *Improving Diagnosis in Health Care*. The authors proposed a systems view of diagnostic errors, with the recognition that accurate and timely diagnosis cannot be made without access to the care team (Figure 11.6). Pediatricians must envision the health care system from the patients' and families' point of view and recognize opportunities to improve the likelihood that children who need the first contact are able to benefit from the team's care.

First Contact

A first contact in a pediatric medical home may be a visit for an acute or chronic health issue or for a well visit. Using a systems view, the pediatrician should consider how excellence in this first contact would be defined by patients and their families. In addition to the patient-physician relationship and cultural effectiveness (see Chapters 8 and 57), patients and families might prioritize a focus on needs, desires, and goals unique to the child and/or family. Pediatricians might also include screening for poverty and for financial harm from medical treatment. Currently, this first contact may be with another care team member via a nurse triage telephone call or via an online patient portal message.

Longitudinal Care

Longitudinal care requires providing optimal care over time to individual patients and to populations of patients, ideally within the medical home model. The Joint Principles of the Patient-Centered Medical Home (PCMH) were co-published in 2007 by the AAP, American Academy of Family Physicians, American College of Physicians, and the American Osteopathic Association. An emphasis on the Triple Aim and the change in payment models (from fee-for-service to payment for value) have helped fuel this population health approach. Care is no longer limited to face-to-face physician visits and phone triage with nurses; it includes nonvisit care via electronic patient portals between in-person visits to address simple new concerns, determine if a visit is necessary, provide test results, and follow up with patients and families on chronic health issues.

The AAP aptly describes the population health mindset as a change by health professionals from passivity to proactivity. Rather than waiting for patients to come to providers and care teams, the care teams reach out to patients and families. Not all patients in a given practice have the same level of need; thus, different systems approaches are necessary. Relatively healthy patients benefit from preventive interventions (eg, immunizations) and screenings (eg, review of growth at well visits, lead and developmental screenings). Children with a single chronic disease (eg, persistent asthma) may benefit from practice-level processes to improve their health outcomes by targeting identification of emergency department visits, monitoring oral steroid use, and regularly updating asthma action plans. For children with medical complexity, care management may be necessary to help families and the PCMH team optimize the value of care rendered (eg, assigning a primary nurse who knows the child well and who can triage concerns as they arise).

The National Resource Center for Patient/Family-Centered Medical Home (formerly the National Center for Medical Home Implementation), a collaboration between the AAP and the Maternal and Child Health Bureau of the Health Resources and Services Administration of the US Department of Health and Human Services, summarized a number of promising practices and their PCMH innovations, including family orientation and integration of comprehensive care.

Family Orientation

Children and their caregivers will not achieve optimal health or have an optimal experience of care unless pediatricians and their care teams are deliberate in their commitment to systematic culturally competent and effective care, both for individual patients and groups

Table 11.2. Examples of Opportunities to Increase Health Care Value for Patients and Families

Care Opportunity	*Individual Patient (and Family)*	*Microsystem*	*Mesosystem/Macrosystem*
Pre–first contact	Pre-visit contact (electronic or paper) soliciting the family's initial health concerns and the family's story that they want to share with the team in advance	Open access scheduling Expanded clinic hours Website or other electronic presence to welcome families and explain resources	Decrease barriers to transitioning new patients from inpatient settings (eg, neonatal intensive care unit, hospital) into the medical home model
First contact (ie, first clinic visit)	Culturally competent care (see Chapters 8 and 57) Routine inclusion of the question "What matters to you?" at the first visit[a]	Screening for mental health issues in pediatric patients (eg, PHQ-9M for patients age 12–17 years) and in mothers of infants (eg, postpartum depression screening) Adverse childhood experiences screening Food scarcity screening	Strategies to decrease wait times and increase efficiency of the visit from the family's perspective
Longitudinal care	Advocacy (eg, with school system for IEP) for health needs Health coaching Steps 1–4 in high value care framework (see Figure 11.6)[b]	Step 5 in high-value care framework (QI): Identify systems-level opportunities to improve value (see Figure 11.6)[b] Non-visit care (eg, online portal) Care management for patients such as those with complex presentations, asthma, or depression Identification of and contact with high-risk children needing the influenza vaccine	Strategies to improve transitions of care to adult providers for young adults with medical complexity across pediatric primary care, adult primary care, and specialty groups Strategies to collaborate on matters of school-related health, such as with coaches for concussion services, school staff about meals and nutrition, and in-school influenza vaccine clinics
Family orientation	Shared decision making that incorporates patient and family preferences, values, and context (ie, circumstances)[c]	Needs assessments of families in the practice in terms of issues such as preferred communication and extended hours	Advocate for needs assessments of families in other areas of multispecialty practices
Integration of comprehensive care	Use of handoff tool with accepting physician when a patient is admitted to the hospital or to another new care team	Registered nurse care management program with registry for medically complex children Electronic tool for communicating patient care goals between patient, family, and health care teams	Work with inpatient and outpatient specialty, emergency department, and hospital colleagues to improve transitions of care and patient safety when patients move from 1 setting to another

Abbreviations: IEP, Individualized Education Program; PHQ-9M, 9-item Patient Health Questionnaire Modified for Teens; QI, quality improvement.

[a] Institute for Healthcare Improvement. What matters? IHI.org website. www.ihi.org/Topics/WhatMatters/Pages/default.aspx. Accessed August 19, 2019.

[b] Modified from Smith CD; Alliance for Academic Internal Medicine–American College of Physicians High Value, Cost-Conscious Care Curriculum Development Committee. Teaching high-value, cost-conscious care to residents: the Alliance for Academic Internal Medicine–American College of Physicians Curriculum. *Ann Intern Med*. 2012;157(4):284–286.

[c] Hoffmann TC, Montori VM, Del Mar C. The connection between evidence-based medicine and shared decision making. *JAMA*. 2014;312(13):1295–1296.

of patients. Care team members must have knowledge of the social determinants of health and their effect on health (see Chapter 141). This is particularly important when establishing a strong relationship with children and their caregivers at the first visit.

Integration of Comprehensive Care

Integration of comprehensive care requires pediatricians and their PCMH team members to integrate the care of patients within the PCMH and across other parts of each patient's health ecosystem to ensure that data are shared appropriately and handoffs occur effectively. This includes the interaction between primary and secondary (or specialty) care (see Chapter 1). Several new care delivery innovations include electronic specialty consults as well as integrated behavioral health and other specialty care models integrated within the PCMH. It also includes integration as part of ongoing care (eg, in conjunction with community partners, such as public health, schools, child care centers, home health and nursing agencies, and pharmacies).

To Err is Human, published in 1999 by the Institute of Medicine (now the Health and Medicine division of the National Academies), catalyzed the US patient safety movement. A critical component of safe care is the expert and deliberate process for communicating with teams and across teams at times of transition. This includes transitions across care settings during an episode of care (eg, emergency department to

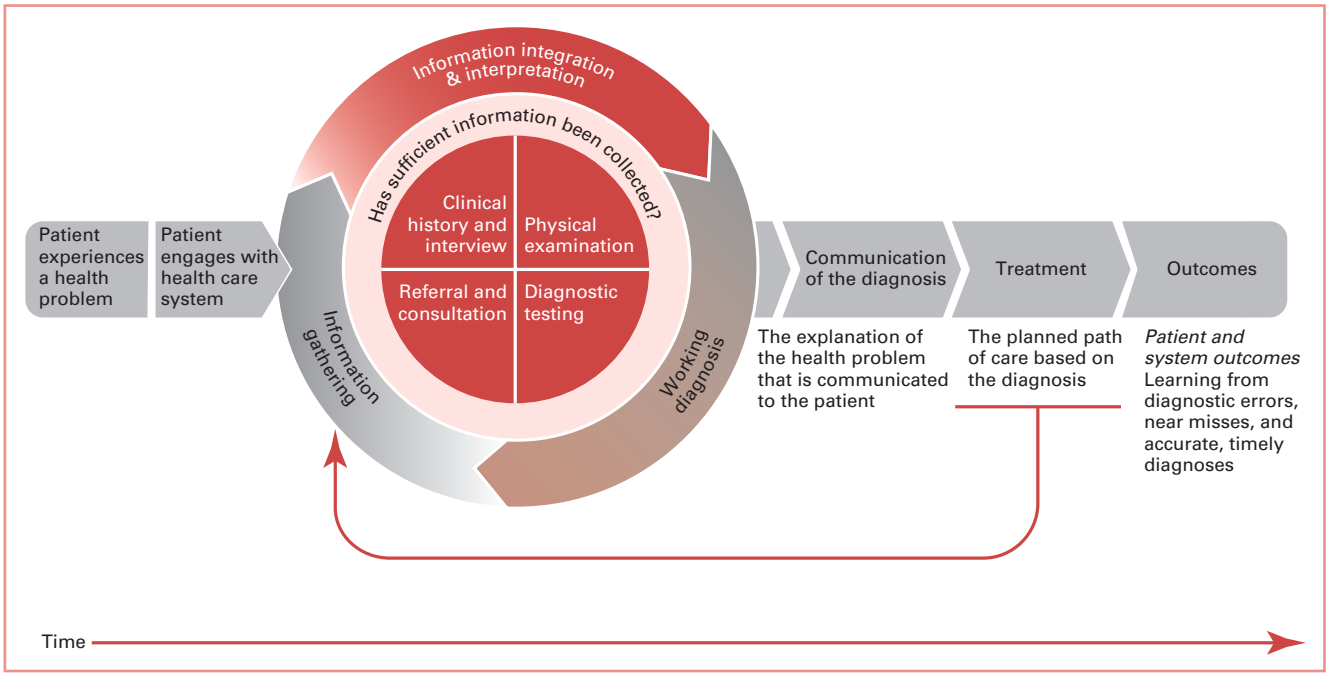

Figure 11.6. The diagnostic process.

Reprinted with permission from National Academies of Sciences, Engineering, and Medicine. *Improving Diagnosis in Health Care.* Washington, DC: The National Academies Press; 2015. https://doi.org/10.17226/21794.

hospital, hospital to PCMH, PCMH to specialty care). The Agency for Healthcare Research and Quality Team STEPPS program provides a model for training in interprofessional teams to improve patient safety. The I-PASS program is a framework studied in pediatric residencies to increase patient safety during provider handoffs. Common handoffs in integrated, comprehensive care include dismissal of patients with complex medical issues from an acute care hospital setting to the PCMH.

Pediatric Primary Care Examples of Health Systems Science Principles

Advocacy

Advocacy has long been a professional expectation of pediatricians on behalf of children, a segment of society without a legal voice. Advocacy occurs at the individual patient-pediatrician level (eg, working with schools to evaluate students who may qualify for special education services) or at a higher level (eg, the state legislature for effective booster seat laws). Carol Berkowitz, MD, has described advocacy for individual patients as advocacy with a "little a," and for groups of patients as advocacy with a "big A."

Systems thinking can help reveal opportunities to advance child health in the realm of advocacy. For example, pediatricians can use the AAP Oral Health Toolkit to advance oral health initiatives for children at multiple levels of the system, including the community. Alternatively, if during a face-to-face clinic visit a pediatrician notes findings that are suspicious for child abuse and maltreatment, the pediatrician is legally bound to advocate for the child by reporting to Child Protective Services. Pediatricians can work with their clinical (ie, microsystem) team to develop new strategies for making children more comfortable during visits when suspected abuse is the chief concern. They can work with community partners to ensure child-friendly handoffs to those conducting forensic interviews and to educate child caregivers on reporting requirements and parents on abuse prevention strategies (ie, macrosystem). Conceptualizing the system in this manner may also help pediatricians consider the stakeholders who can align with their efforts and/or inform their efforts to help ensure success.

Population Health

As mentioned previously, 1 intervention to improve pediatric health is care coordination of children with complex health needs. In 2014, the AAP published recommendations for care coordination of children with medical complexity, including features of care coordination excellence, such as use of health information technology and health outcomes tracking over time. This recommendation was reaffirmed in 2018. As with many population health strategies, the perspective focuses on the health of all patients empaneled to the PCMH, not just those who come in for face-to-face visits.

Recent years have seen several successful population health models within primary care settings, including collaborative care models for adolescent depression and other integrated behavioral health strategies. Primary care pediatricians have collaborated with pediatric subspecialists and nurse care managers using patient registries to proactively care for their population of children and adolescents with persistent asthma. Registries can also be helpful to proactively manage children with medical complexity and children with other chronic conditions, such as attention-deficit/hyperactivity disorder.

Social Determinants of Health

As previously noted, social determinants of health (see Chapter 141) are estimated to have a more significant effect on health than health behaviors, health care, or genetics. Pediatricians must

elicit information about social determinants of health to be successful in caring for individual patients. At the microsystem level and above within the health system, pediatricians and their care teams can use population health approaches to identify subpopulations of patients in their practice (eg, refugee families) and conduct a needs assessment to tailor the practice to meet the needs of these patients.

Beyond the health system, many opportunities exist for pediatricians and other child health advocates to influence change to minimize the negative effect of social determinants of health. The Centers for Disease Control and Prevention developed the "Health Impact in 5 Years" initiative, which highlights nonclinical, community-wide strategies (Figure 11.7). These evidence-based strategies report positive health impacts within 5 years, and cost effectiveness and/or cost savings over the lifetime of the population.

High-Value Care

The role and limitations of laboratory tests and other diagnostic studies in making an accurate diagnosis for patients and families has long been taught as part of the basic and clinical sciences. With a systems approach, the NASEM model for improving diagnoses emphasizes diagnoses as a series of hypothesis testing (see Figure 11.6). For example, the diagnosis of acute otitis media is made based on history and physical examination alone. A patient presenting with a limited diet and fatigue may require only 1 laboratory test (ie, complete blood count) to confirm iron deficiency anemia. Many diagnoses are made over time, however.

In 2012, the Alliance for Academic Internal Medicine and the American College of Physicians published a 5-step model for teaching high-value care to residents (Figure 11.8). These evidence-based strategies report positive health impacts within 5 years of implementation and are cost effective and/or cost saving over the lifetime of the population. They can help pediatricians see the relationships across the key HSS-related knowledge and concepts of evidence-based medicine, shared decision making, and health care improvement.

Steps 1 and 3 of the model are part of critical appraisal of the literature and evidence-based medicine. Step 2 provides an opportunity for pediatricians to stop medications or reconsider unnecessary testing if it does not provide value to the patient. Step 4, which is part of shared decision making, requires pediatricians to apply what they have learned from the evidence to the patient in front of them. More broadly, this is the stage at which shared decision making, whether formal or informal, is necessary to ensure that the patient (as age allows) and family are given adequate information to make a decision that reflects

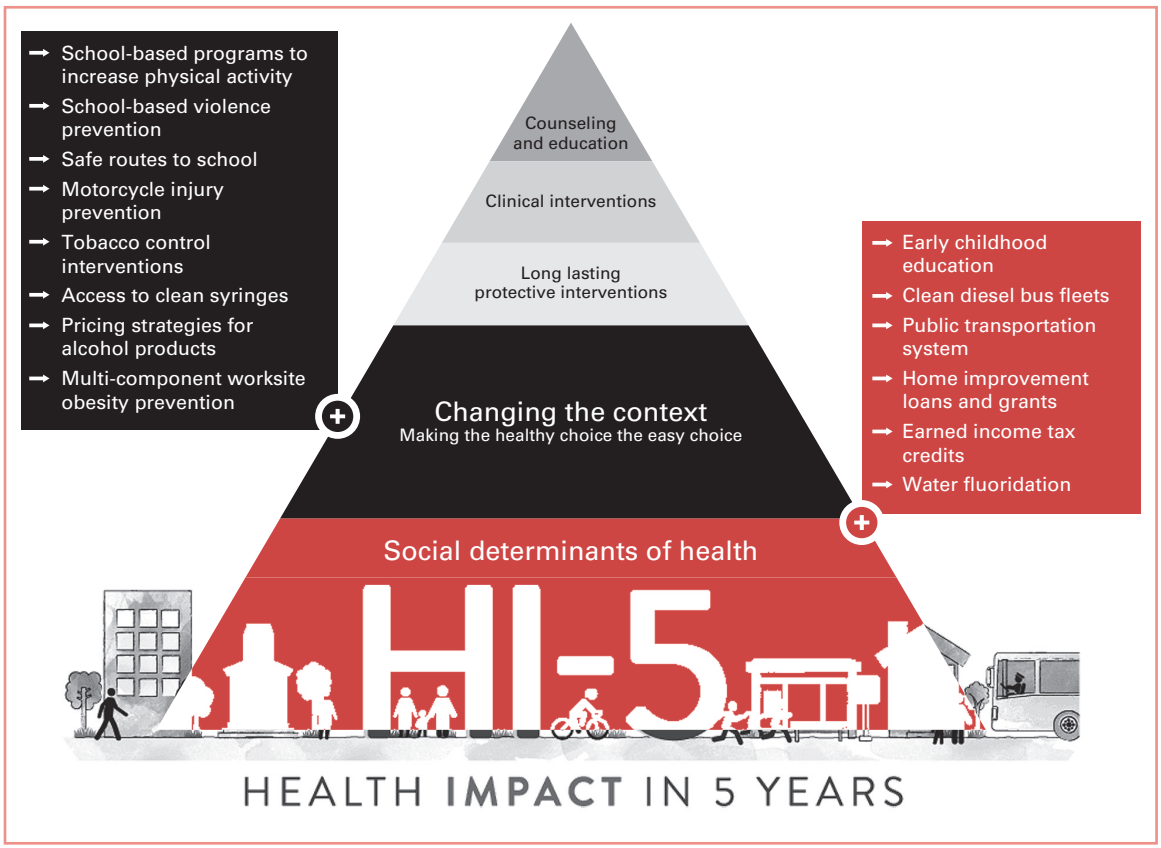

Figure 11.7. Public health impact pyramid. The pyramid depicts the potential impact of different types of public health interventions from greatest potential impact at the base (because they reach entire populations of people and require less individual effort) to least potential impact (because they target specific populations and require more individual effort).

Reprinted from Centers for Disease Control and Prevention, Office of the Associate Director for Policy and Strategy. Health Impact in 5 Years. CDC.gov website. www.cdc.gov/policy/hst/hi5/index.html.

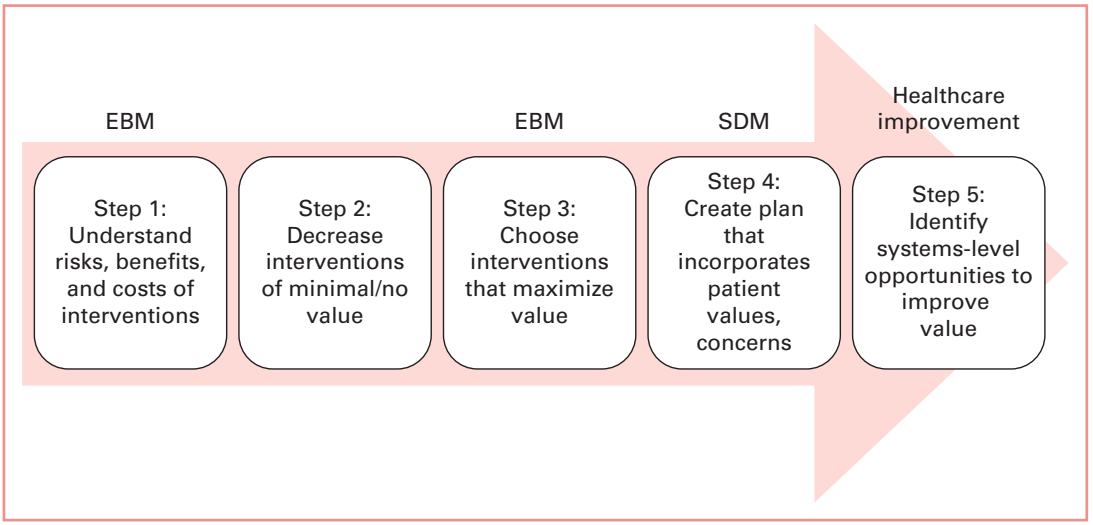

Figure 11.8. Framework for teaching high-value care, showing some of the relationships to other health systems science–related concepts.
Abbreviations: EBM, evidence-based medicine; SDM, shared decision-making.
Adapted with permission from Smith CD; Alliance for Academic Internal Medicine–American College of Physicians High Value, Cost-Conscious Care Curriculum Development Committee. Teaching high-value, cost-conscious care to residents: the Alliance for Academic Internal Medicine–American College of Physicians Curriculum. *Ann Intern Med*. 2012;157(4):284–286.

their context (eg, other aspects of their lives they are balancing as a family, the work of being a patient), their preferences, and their values. Step 5 is health care improvement at the microsystem level or above, that is, QI or safety efforts to increase value for multiple patients.

Physicians may need help determining which tests to order using a high-value approach that reflects the individual considerations for each patient while also reflecting what is known to be effective care. Choosing Wisely collaborated with the AAP to identify 10 tests or treatments that pediatricians should question (Box 11.1).

Box 11.1. Ten Things Physicians and Patients Should Question

1. **Antibiotics should not be used for viral respiratory illnesses (sinusitis, pharyngitis, bronchitis and bronchiolitis).** Antibiotics should not be used for upper respiratory illnesses characterized by congestion, cough, or pharyngeal pain unless criteria for bacterial sinusitis or Group A streptococcal pharyngitis are met. The vast majority of these infections are caused by viruses.

   Respiratory infections account for the majority of antibiotic prescriptions for children, and it is estimated that 50% of antibiotic prescriptions for respiratory infections in children are unnecessary. Antibiotic use for viral respiratory illnesses not only leads to higher healthcare costs and more adverse events, but also can lead to antibiotic resistance.
2. **Cough and cold medicines should not be prescribed, recommended, or used for respiratory illness in young children.** Research has shown these products offer little benefit to young children and can have potentially serious side effects. Many cough and cold products for children have more than one ingredient, increasing the chance of accidental overdose if combined with another product.
3. **Computed tomography (CT) scans are not necessary in the immediate evaluation of minor head injuries; clinical observation/ Pediatric Emergency Care Applied Research Network (PECARN) criteria should be used to determine whether imaging indicated.**

   Minor head injuries occur commonly in children and adolescents. Approximately 50% of children who visit hospital emergency departments with a head injury are given a CT scan, many of which may be unnecessary. Unnecessary exposure to x-rays poses considerable danger to children including increasing the lifetime risk of cancer because a child's brain tissue is more sensitive to ionizing radiation. Unnecessary CT scans impose undue costs to the health care system. Clinical observation prior to CT decision-making for children with minor head injuries is an effective approach.
4. **Neuroimaging (CT, MRI) is not necessary in a child with simple febrile seizure.** Imaging, including head CT, brain MRI, and skull films are associated with some risk and do not help with diagnosis or treatment of simple febrile seizures. MRI is associated with risks from required sedation and high cost. Head CTs can slightly increase the long-term risk for cancer.
5. **Computed tomography (CT) scans are not always necessary in the routine evaluation of abdominal pain.** CT imaging in the emergency department evaluation of children with abdominal pain is frequent and can be inconsistently used, including overused. While radiation is necessary to perform a CT scan, there is both misunderstanding and often concern about the radiation necessary and the debate over the potential long-term development of cancer from this radiation. There also is the potential for

Box 11.1. Ten Things Physicians and Patients Should Question *(continued)*

an unnecessary amount of radiation from inappropriately performed CT examinations, as there are unique approaches and considerations with CT examinations in children that allow for lower radiation doses. CT can be very valuable in the setting of pediatric abdominal pain, but only when it is the correct test to do at the time (as opposed to waiting, or using another test that does not depend on ionizing radiation especially ultrasound), and performed in the right way (child-sized CT techniques).

6. **Don't prescribe high-dose dexamethasone (0.5 mg/kg per day) for the prevention or treatment of bronchopulmonary dysplasia in preterm infants.** High-dose dexamethasone (0.5 mg/kg day) does not appear to confer additional therapeutic benefit over lower doses and is not recommended. High doses also have been associated with numerous short- and long-term adverse outcomes, including neurodevelopmental impairment.
7. **Don't perform screening panels for food allergies without previous consideration of medical history.** Ordering screening panels (IgE tests) that test for a variety of food allergens without previous consideration of the medical history is not recommended. Sensitization (a positive test) without clinical allergy is common. For example, about 8% of the population tests positive to peanuts but only approximately 1% are truly allergic and exhibit symptoms upon ingestion. When symptoms suggest a food allergy, tests should be selected based upon a careful medical history.
8. **Avoid using acid blockers and motility agents such as metoclopramide (generic) for physiologic gastroesophageal reflux (GER) that is effortless, painless, and not affecting growth. Do not use medication in the so-called "happy-spitter."** There is scant evidence that gastroesophageal reflux (GER) is a causative agent in many conditions though reflux may be a common association. There is accumulating evidence that acid-blocking and motility agents such as metoclopramide (generic) are not effective in physiologic GER. Long-term sequelae of infant GER is rare, and there is little evidence that acid blockade reduces these sequelae. The routine performance of upper gastrointestinal (GI) tract radiographic imaging to diagnose GER or gastroesophageal disease (GERD) is not justified. Parents should be counseled that GER is normal in infants and not associated with anything but stained clothes. GER that is associated with poor growth or significant respiratory symptoms should be further evaluated.
9. **Avoid the use of surveillance cultures for the screening and treatment of asymptomatic bacteriuria.** There is no evidence that surveillance urine cultures or treatment of asymptomatic bacteriuria is beneficial. Surveillance cultures are costly and produce both false positive and false negative results. Treatment of asymptomatic bacteriuria is harmful and increases exposure to antibiotics, which is a risk factor for subsequent infections with a resistant organism. This also results in the overall use of antibiotics in the community and may lead to unnecessary imaging.
10. **Infant home apnea monitors should not be routinely used to prevent sudden infant death syndrome (SIDS).** There is no evidence that the use of infant home apnea monitors decreases the incidence of SIDS and should not be used routinely for this purpose; however, they might be of value for selected infants at risk for apnea or cardiovascular events after discharge.

Reprinted with permission from American Academy of Pediatrics. Ten things physicians and patients should question. ChoosingWisely.org website. www.choosingwisely.org/societies/american-academy-of-pediatrics.

Summary and Future Challenges in Health Systems Science

The knowledge, skills, and perspectives needed by pediatricians to effectively improve and maintain the health of children will continue to rapidly change in the coming decades, and health professionals must be able to envision the need for basic science, clinical science, and HSS to help all children realize their potential. The pace of change in pediatric trainee education and continuing professional development must align with that of the practice and society. The professional identity of pediatricians and other health professionals must focus on caring for patients and their families, for populations of patients, and for the system. Advancements in medical education concerning best practices in HSS education (for undergraduate medical education, graduate medical education, and continuing professional development) must evolve in a way that is authentic and meaningfully integrated with the work of interprofessional care teams. Finally, health services research, a topic that is beyond the scope of this chapter, must continue to elucidate best means of ensuring that high-value care occurs the first time, every time in a manner that complements the context, preferences, and values of the patient and family.

CASE RESOLUTION

You respond to the family's request for imaging using the guidance of the American College of Physicians for these conversations. You determine the perspectives of Sara and her mother ("What are you afraid we will find?" and "What do you think is going on, and what are you worried about?"); explain your reasoning for not recommending imaging ("The good news is that you do not have any worrisome symptoms."); make it clear that you are on Sara's side ("I wish more testing could help you, but it can actually make things worse."); and make a clear follow-up plan and review red flag signs and symptoms ("I want to see you in 2 weeks, but contact us sooner if there are changes that concern you.").

With your understanding of HSS-related concepts, such as social determinants of health and how system issues can negatively affect health, you work with your clinical (ie, microsystem) team to connect Sara's mother to a community health worker. The health worker meets with Sara and her family in their home to learn more about some of the challenges they are experiencing in accessing basic necessities as well as the health care system. The health worker connects Sara's mother to a primary care provider to help her address her own chronic illnesses and helps Sara's family access county services for housing and food. Your clinical team decides to initiate a QI project with the goal of reducing the number of missed follow-up visits for pediatric patients. In the course of the project, your team develops a care management approach for children with multiple chronic diseases. As part of your successful project, you begin screening for adverse childhood experiences to better recognize their effect on health, and several colleagues in your practice share what you have learned with the local health department and school system.

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CHAPTER 12

Population Health for Pediatricians

Michael Weiss, DO, FAAP

CASE STUDY

You are preparing to see a patient familiar to your practice for an acute visit. You have not seen her for 11 months and, as you review the chart, you recall that the child is 5 years old and was born with a myelomeningocele at L4-5. She underwent surgery as an infant with placement of a ventriculoperitoneal shunt and gastrostomy tube. She has used a motorized wheelchair for 2 years and requires intermittent urinary bladder catheterization. Generally, she has done well and continues to see specialists in gastroenterology, neurosurgery, neurology, and urology. She attends public school, where she has an Individualized Education Program; receives occupational, speech, and physical therapy; and qualifies for in-class assistance. On further review, you note she is insured by your local Medicaid managed care plan and you receive a monthly capitation payment for her care in addition to potential value-based incentives around certain quality indicators.

Questions

1. What are the specific challenges associated with caring for this child?
2. How do you begin to organize her multiple special needs?
3. What are the clinical implications of the methodology by which you are paid for her care?
4. What strategies can you use to ensure this child receives the entirety of care required for her to thrive?
5. Who is your team?

Population Health: What and Why?

Population health has been defined in many ways. In simple terms, population health is about keeping a defined population healthy through proactive, preventive measures that minimize fragmented, inefficient care and improve clinical outcomes while reducing the overall cost of care.

During pediatric training and throughout their career, pediatricians appropriately spend most of their time developing and refining the knowledge and technical skills required to provide high-quality care to patients. Pediatricians learn about disease, enhance communication skills, and learn procedures, such as endotracheal intubation, lumbar puncture, and intravenous catheter placement techniques.

Over the past 3 to 4 decades, increasing emphasis has been placed on understanding how effective and efficient our delivery of health care is and how we measure these outcomes. This new focus filters down to frontline pediatricians, who must develop a clear understanding of much more than clinical care. Pediatricians need to understand health care payment methodologies, clinical quality metrics, care model design improvements, and care coordination programs. A fundamental understanding of these concepts is now a vital component of successfully caring and advocating for infants, children, adolescents, and young adults. This chapter reviews some of the main population health concepts and facilitates the successful navigation of the complex health care system, helping pediatricians provide improved care for their patients and families.

In the frequently quoted works, *To Err Is Human* and *Crossing the Quality Chasm,* the Institute of Medicine (now known as the Health and Medicine division of the National Academies) brought to light the prevalence of preventable medical errors and the disparity in quality of care across the United States. These reports estimated that 44,000 to 98,000 preventable deaths annually at a cost between $17 billion and $29 billion attributable to lost income and additional care necessitated by errors. Further, Institute of Medicine concluded that "The U.S. health care delivery system does not provide consistent, high-quality medical care to all people." In 2009, Atul Gawande, MD, MPH, a Boston-based surgeon and health policy researcher, published "The Cost Conundrum," in which he brought to light the wide variation in health care spending and outcomes across the United States. For 1 region in south Texas, he pointed to nearly double the national average per-capita spending on health care with no demonstrable improvements in quality versus the rest of the country. This, along with data from the Commonwealth Fund (Figures 12.1 and 12.2), brought to the public eye that the trajectory of health care spending in the United States was unsustainable and, more importantly, that patients were not receiving better-quality care

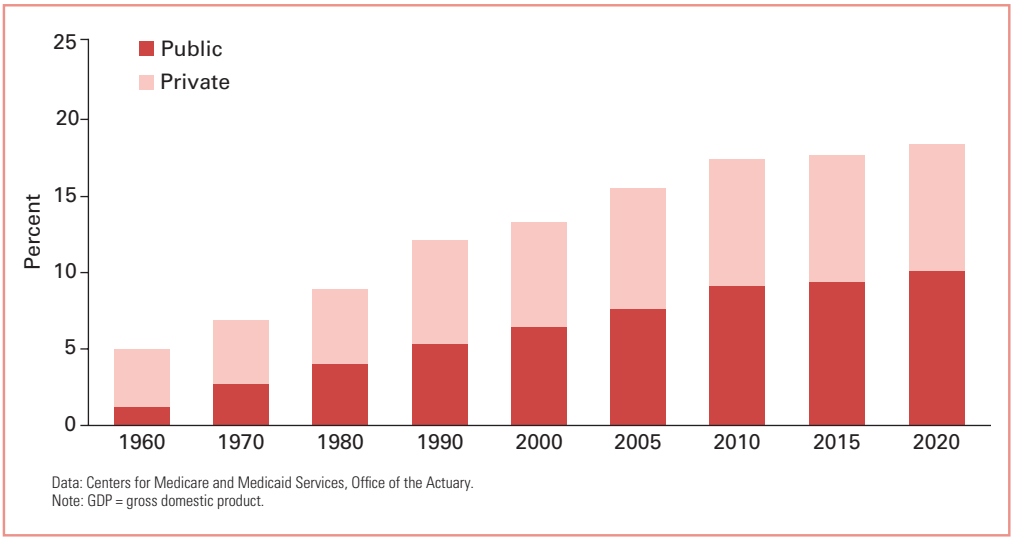

Figure 12.1. Growth in health spending as a share of the economy.
Reprinted with permission from Lambrew JM. Getting ready for health reform 2020: what past presidential campaigns can teach us. The Commonwealth Fund website. www.commonwealthfund.org/publications/fund-reports/2018/jun/getting-ready-health-reform-2020-presidential. Published June 26, 2018. Accessed August 22, 2019.

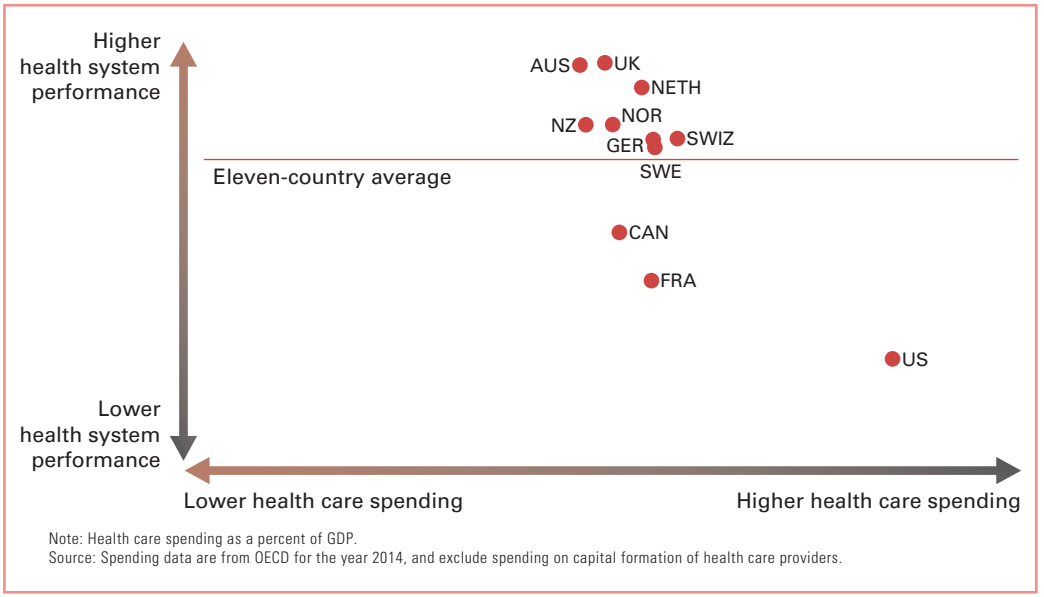

Figure 12.2. Health care system performance compared with spending.
Reprinted with permission from Schneider EC, Sarnak DO, Squires D, Shah A, Doty MM. Mirror, mirror 2017: international comparison reflects flaws and opportunities for better U.S. health care. The Commonwealth Fund website. www.commonwealthfund.org/publications/fund-reports/2017/jul/mirror-mirror-2017-international-comparison-reflects-flaws-and. Published July 14, 2017. Accessed August 22, 2019.

as a result of the spending. Subsequently, the notion of the Triple Aim of better health for populations, better care experiences, and lower per-capita costs was introduced by the Institute for Healthcare Improvement (and more recently enhanced by others to become the Quadruple Aim by adding joy of practice). The concept of accountable care organizations then evolved from the Patient Protection and Affordable Care Act. This framework has served as the template for population health work across the country, in which the focus is on caring for populations of patients with proactive, team-based care, using accurate and timely data to effect positive clinical and service-based outcomes (see Chapter 21).

Health Care Payment Methodology and Practice

A basic understanding of the funding stream for the care patients receive is an important step toward improving quality, care coordination, and clinical outcomes. By far, the largest payers for children's health care in the United States are Medicaid and the Children's Health Insurance Program (CHIP), which cover nearly 30 million and 9 million children, respectively. Children qualify for the programs based on the income level and the number of members in their family. Qualifications vary by state and are usually based on a

percentage of the federal poverty level. CHIP serves as a supplement to assist those families who may not qualify for Medicaid. Coverage for basic care, called early and periodic screening, diagnosis, and treatment, or EPSDT, such as immunizations, developmental screening, and health maintenance visits, is mandated by these programs.

Private insurers make up most of the remaining payers. Private payment may occur through a preferred provider organization (PPO) or a health maintenance organization (HMO). With a PPO plan, patients are usually able to access any health professional covered by their insurance without the need for a specific referral that would be reviewed for clinical necessity in an HMO. High-level procedures and interventions may still require approval before they can be completed (eg, magnetic resonance imaging scans, surgeries). In an HMO plan, patients are encouraged to access their chosen or assigned primary care professional (PCP) for most conditions. If the PCP believes specialty care is required, an authorization request is generated and reviewed by the health plan for medical necessity before the patient can access the specialty care. Much debate exists over the preferred approach, as each has positive and negative components. The PPO provides more freedom of choice and ease of access, while the HMO creates an accountability and actionable data stream to the PCP of who serves as the medical home for patients. Data from regions where HMOs have been prevalent for some time show that quality and cost containment are enhanced in the HMO environment.

Within these insurance coverages there are also a variety of methods whereby payment to health professionals and hospitals can be made. In the traditional approach, known as fee for service, a health professional is paid based on a prearranged fee schedule for each encounter that occurs. Bundled payments, which are less common in pediatrics (particularly in the ambulatory setting), are set payments that are made for episodes of care. For example, for a joint replacement procedure, a bundled payment would include preoperative evaluation, surgery (including any required hardware), and postoperative care, including physical therapy and any durable medical equipment.

In the new accountable care paradigm, models involving population-based payment, also known as *capitation,* are much more prevalent. In these models, health professionals are paid a fixed per-member, per-month fee for caring for their patients. One advantage of this methodology is that patient attribution is very clear (addressed later in this chapter). Regardless of the number of times a patient is seen, the monthly payment for services is fixed. This model is aligned with population health principles in that prevention and proactive care are emphasized to create better quality and keep health care costs in check. In these models, services such as immunizations, mental health, and injectable medications are often carved out of the monthly payment and paid for on a fee-for-service basis due to the high cost involved.

As a complement to these payment methodologies, especially with a population-based payment approach, value-based care is being universally incorporated. This usually involves additional financial incentives for demonstrating clinical quality outcomes and appropriate resource use for a defined population for which the health professional is responsible. (Quality metrics are explored later in this chapter.)

The bottom line for pediatricians is to take the initiative to recognize the specifics of how their population of patients is being funded and implement strategies to ensure clinical and operational success. This understanding allows pediatricians to provide the best possible care for patients, advocate for appropriate and comprehensive pediatric-specific insurance coverage, and meet the business requirements of a practice.

Understanding Quality Metrics

Defining clinical quality in medicine has been a long-standing challenge. It has been defined as identifying the correct diagnosis and initiating appropriate treatment that results in resolution of the condition. It has also been defined as the receipt of a prompt appointment with the physician of choice in a friendly, welcoming environment, followed by timely communication and follow-up. Both outcomes are part of the quality spectrum because clinical success and service excellence are dually important.

The other challenge has been how to identify pediatric-specific metrics that are clinically meaningful and objectively measured, and which interventions by the physician responsible for the patient can effect positive change. Measures have evolved over time from process focused to outcome focused, with new emphasis on patient-reported outcome measures (Table 12.1). Clearly, the emphasis of various interventions is on the ultimate benefit to the patient, rather than completion of the intervention itself.

Table 12.1. Categories of Quality Metrics

Measure Type	*Description*	*Example*
Structure	Sufficiency of resources and proper system design	Proper use of a certified EHR
Process	Assesses the interaction between the patient/family and practitioner. Describes the means by which services are delivered	Completing a HbA_{1c} test for a patient with diabetes Completing a scheduled health supervision visit Use of evidence-based guidelines
Outcome	Assesses the effect the care delivered has on clinical outcomes	Number of hospitalizations for a specific condition (eg, asthma)
Patient-reported outcome	Status of a patient's health condition that comes directly from the patient or family	School absenteeism Ability to participate in typical social activities or sporting events
Patient experience	Patient or parent questionnaires addressing their experience with the care they received	CAHPS survey Can be hospital focused or ambulatory physician focused

Abbreviations: CAHPS, Consumer Assessment of Healthcare Providers and Systems; EHR, electronic health record; Hb, hemoglobin.

There are several evidence-based, nationally accepted pediatric Healthcare Effectiveness Data and Information Set (HEDIS) measures that are endorsed by the National Committee for Quality Assurance, National Quality Forum, Pediatric Quality Measure Program, and others. Each measure shares a similar format that includes a description of the clinical issue being addressed, patient inclusion and exclusion criteria, and documentation and coding requirements (Table 12.2). These measures are often part of value-based payment programs sponsored by health plans and organized medical groups and, in the information superhighway era, may be cited in the public domain to compare physicians, hospitals, and medical groups to national or local benchmarks.

Quality metrics are not without limitations. For almost every measure there are certain nuances that may pose potential challenges. For example, in the Appropriate Treatment of Children With Upper Respiratory Infection (URI) measure (see Table 12.2), a child may be seen by the primary care physician, diagnosed with a viral URI, and appropriately *not* given an antibiotic. Later the same day, the family may seek care by another primary care physician, who prescribes an antibiotic, and the child is now viewed as out of compliance with the measure. The physician with accountability acted appropriately but does not receive the correct credit for doing the right thing.

A second general category of quality metrics revolves around appropriate use of clinical resources. Measures in this domain typically include the frequency of emergency department (ED) visits, use of high-cost imaging studies (ie, magnetic resonance, computed tomography), or inpatient admissions for so-called ambulatory-sensitive conditions. For instance, ED visits for asthma may be preventable if a child is appropriately prescribed an inhaled corticosteroid, educated on proper spacer use, and given an asthma action plan. Appropriate resource metric results are typically compared with regional or national benchmarks.

Another category of quality metrics revolves entirely around patient and family experience (previously referred to as patient satisfaction). Typically, patients receive a written or telephone-based survey to assess the perceived level of care they received. The standardized Consumer Assessment of Healthcare Providers and Systems Clinician and Group (CG-CAHPS) survey is most commonly employed. Questions cover multiple domains that address service, timeliness of care, communication, and shared decision making. A representative CG-CAHPS question is: "Did your provider explain things in a way that was easy to understand?"

Greater emphasis in this area is demonstrated by the fact that most value-based programs include patient and family experience as up to 30% of the overall rating of a health professional.

Understanding these metrics, how they can be used to improve care, and how to address the technical and operational challenges associated with them is now an imperative for pediatricians in all disciplines. These metrics have additional utility, as they relate to office-based quality improvement activities and Maintenance of Certification.

Care Coordination Fundamentals

In 1967 the American Academy of Pediatrics first described the notion of the patient-centered medical home. Subsequently, in 2007, a joint statement endorsing the medical home concept was published by the American Academy of Pediatrics, American Osteopathic Association, American College of Physicians, and American Academy of Family Physicians. The patient-centered medical home concepts were updated in 2017 (Box 12.1). Cooley et al cited enhanced pediatric medical home capabilities as a harbinger of improved quality and lower cost of care. With the increasing demands of electronic health records (EHRs), quality metric performance, and other administrative duties, understanding and implementing appropriate care model design principles into one's practice is a necessity. Four such concepts are patient attribution, risk stratification, use of data and analytics, and the care team.

Table 12.2. Example Healthcare Effectiveness Data and Information Set Measure Specifications

HEDIS Measure	*Description*	*Specification*	*Definition*	ICD-10-CM *Codes*[a]
Appropriate Treatment of Children With Upper Respiratory Infection (URI)	Measure evaluates the percentage of children aged 3 months to 18 years who were given a diagnosis of URI and were *not* dispensed an antibiotic prescription.	• Patients with an outpatient or ED visit with a single diagnosis of URI and *not* prescribed an antibiotic on, or 3 days after, the date of the URI diagnosis. • Ensure any secondary diagnoses indicating the need for an antibiotic are submitted on the claim.	• Acute nasopharyngitis • Acute laryngopharyngitis • Acute URI	• **J00** • **J06.0** • **J06.9**
Well-Child Visit 3–6 Years (WC34)	Measure documents at least 1 well-child (health supervision) visit with the primary care physician during the measurement year.	Visit includes a health and developmental history, physical examination, health education, and anticipatory guidance.	Services specific to an acute or chronic condition do not count toward this measure.	• **Z00.110** • **Z00.01** • **Z00.121** • **Additional codes**

[a] Codes subject to change; current as of 2020.

Abbreviations: ED, emergency department; HEDIS, Healthcare Effectiveness Data and Information Set; *ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification*; URI, upper respiratory infection.

Box 12.1. 2017 National Committee for Quality Assurance Patient-Centered Medical Home Concepts

- Team-based care and practice organization
- Knowing and managing your patients
- Patient-centered access and continuity
- Care management and support
- Care coordination and care transitions
- Performance measurement and quality improvement

Adapted from National Committee for Quality Assurance. NCQA PCMH Recognition: Concepts. National Committee for Quality Assurance. www.ncqa.org/programs/health-care-providers-practices/patient-centered-medical-home-pcmh/pcmh-concepts/.

Patient Attribution

A foundational component of care coordination is knowing the patients a pediatrician is responsible for. This knowledge allows for proactive, rather than reactive, approaches to care. For example, knowing which children in the practice have not yet received an appropriate immunization or timely health supervision visit allows the pediatrician to reach out to schedule such care. Attribution is facilitated by the population-based payment paradigm, as compensation is tied to a defined population for which the pediatrician is clinically and financially responsible. In situations in which children are migrating among various physicians, attribution may be further complicated, and various methods have been devised to assist with this process. In such situations, most attribution models emphasize the frequency of primary care health supervision visits to a single pediatrician as the best predictor of responsibility for clinical outcomes for a given child. Attribution need not be dictated by the health plan; internal practice-based attribution can also be a successful approach. The important point is that a pediatrician must know their population to be effective.

Risk Stratification

Once a population is defined, the next step is to stratify the patients to focus efforts on the areas of greatest need. Patients can be stratified by age, medical condition, certain clinical gaps in care, or any other medical or psychosocial determinant. Multiple risk stratification tools have been identified, but their use is limited in the primary care office setting. More commonly, health risk assessment questionnaires are employed for this purpose. High-risk patients can be aggregated and assigned to care coordinators, where available, for close follow-up and care plan oversight. For example, patients in a practice with persistent asthma can be identified, and their care can be reviewed to ensure they are prescribed appropriate inhaled corticosteroids. This risk stratification process does not omit attention to the multiple well children in the practice who require ongoing proactive anticipatory guidance, immunizations, and education.

Use of Data and Analytics

Incorporating the use of data and analytics into practice is essential. These data sources may include health plans, government payers, such as Medicaid, hospitals, EHRs, regional health information exchanges, pharmacy benefit managers, or other sources of aggregated information. The health professional should be aware that these data are often claims based, and there may be a significant lag from the date of care to the actual report. Using this information facilitates proactive, preventive care and offers the ability to assess quality improvement activities. Examples of this type of data include HEDIS performance, ED and inpatient utilization by patients, and appropriate use of antibiotics. Accessing timely, accurate data can be very challenging. It is highly recommended that pediatricians develop partnerships with payers, hospitals, regional health information exchanges, and large physician groups to help aggregate data whenever possible. This approach also allows pediatricians to compare their performance with national and regional benchmarks.

The Care Team

The pediatrician should be focused on diagnostic skills, understanding and implementing appropriate therapies, and nurturing a strong and trusted relationship with patients and families. Unfortunately, the literature clearly demonstrates that physicians are spending more time in activities unrelated to these important competencies. Charting in complex EHRs, filling out forms, calling different clinicians to coordinate care, seeking medical records, and returning low-level calls are a few of the activities that dominate a pediatrician's day. How can this be adjusted to work for the patient and the physician?

In recent years, production improvement programs, such as Taiichi Ohno's Toyota production system, which inspired Lean Manufacturing in the United States, have been applied, very successfully, to medical care. The concept is to avoid waste in all its forms (eg, time), create standard work for all members of the team, and ensure each person is working to the height of their respective training and licensure. (An in-depth review of Lean methodology is beyond the scope of this chapter but highly recommended for additional reading.) For example, a medical assistant should be filling out certain forms under the direction of the medical team, rather than having licensed personnel performing that task. Likewise, a physician should not be searching for medical records or making copies.

The correct application of care team models creates a well-delineated set of roles with clear understanding of who the responsible team member is for each task. The team acts proactively and anticipates the needs of the patient. Approaches such as huddles and visual performance boards facilitate this proactive approach and highlight clinical and service goals and outcomes.

Putting It All Together

The role of the pediatrician has expanded in recent years. Pediatricians must provide the best clinical care possible and are now required to understand a multitude of payment models, quality metrics, and data sources that facilitate such care. A failure to incorporate this broader knowledge base into daily practice can adversely affect outcomes for patients. As advocates for children, the more pediatricians can understand about this new paradigm, the more successful they can be in ensuring that infants, children, adolescents, and young adults are provided the most efficient quality care possible.

CASE RESOLUTION

Your medical assistant performs a pre-visit chart review that includes identification of any potential gaps in care, recent hospitalizations or ED visits, review of specialty notes for updated medication doses, pending laboratory tests or diagnostic testing, and immunization records. The school Individualized Education Program is reviewed to ensure therapies are occurring at the appropriate frequency with associated progress reports demonstrating improvement. During your morning huddle with your care team, you determine that the child has seen 2 of her subspecialists since she last visited your office, so your team updates her medication list and overall care plan to reflect the latest information. You also determine that she is overdue for a health supervision visit, and your staff converts her acute visit today to a such a visit to include her annual influenza vaccine. You note that she has a registered nurse who acts as her case manager, who is provided by her Medicaid managed care program, and ensure that your team connects with the case manager and social worker to help coordinate care and address any social determinants of health that may pose a challenge. During her visit you include the family in all decision making about her care and provide a written summary of the visit and a specific action plan. Your office securely messages the family in 48 hours to reinforce the care plan and ask if there are any other questions.

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CHAPTER 13

Principles of Pediatric Therapeutics

Bonnie R. Rachman, MD

CASE STUDY

An 18-month-old girl who has had a cough, runny nose, and fever for 2 days is brought to your office for evaluation. The previous night she awoke from sleep crying and pulling at her ear. The patient has no other symptoms. Her mother states she has had previous ear infections; the most recent occurred 2 months ago. The last time she took amoxicillin she broke out in hives. Otherwise, the patient has no significant medical history.

On physical examination, the patient is febrile with a temperature of 38.9°C (102°F) and has yellow rhinorrhea. The ear examination reveals a red, bulging, nonmobile tympanic membrane in 1 ear, while the other tympanic membrane appears normal. The remainder of the examination is benign.

Questions

1. What are the current clinical practice guidelines for antibiotic treatment of otitis media? How does treatment change with the age and symptoms of the patient?
2. How does the previous reaction to a medication influence the antibiotic choice?
3. How do factors (eg, parental work, child care) affect administration of the medication?
4. What role do over-the-counter medications have in the management of the patient's symptoms?

A *drug* or *therapeutic* can be defined as any substance that is ingested, absorbed, or injected that alters the body's function. Examples include prescription medications, over-the-counter (OTC) medications, homeopathic preparations, herbal remedies and teas, vitamin supplements, and illicit substances. Different drug categories have differing safety profiles and regulation levels. Prescription drugs are the most regulated. Homeopathic preparations, some vitamin formulations, and most herbal remedies may have little, if any, standardization, safety testing, or regulation. Illicit drugs have no quality testing.

The use of prescription and OTC medications is very common in pediatrics. The Slone Survey, a random digit-dial survey of medication use, found that families with children reported that more than 55% of children younger than 12 years had taken some medication preparation within the last 7 days. Of those taking a medication, 22% were taking at least 1 prescription medication. In a given month, more than 50% of preschool-age children had received some OTC medication. In 2011 to 2012, 7.5% of US children and teenagers aged 6 to 17 years took medication for emotional or behavioral difficulties. The number of children aged 12 years and younger being administered an OTC medication in a given period is more than twice that of a prescription medication. The most commonly used OTC medications are acetaminophen and ibuprofen. In the adolescent age group, aged 12 to 17 years, more OTC products are used for acne and less for allergies or pain relief. Given that the use of OTC medications is so prevalent and that many OTC medications contain multiple active ingredients, concerns about their safety profile for children is an issue that needs to be addressed by pediatricians with families at routinely scheduled office visits as well as by regulatory agencies.

Another concern is the use of prescription or OTC medications as drugs of abuse. Of particular concerns are adolescents who use alcohol, illicit drugs, and medications, including OTC cough medications containing dextromethorphan. In the 2017 Monitoring the Future survey of 8th, 10th, and 12th graders nationwide, approximately 3% of the survey participants reported using OTC cough medicine to "get high" in the past year. Also, in the past year, 49% reported use of alcohol, 28% reported use of marijuana, 61.3% reported use of Vicodin, and 1.9% reported use of oxycodone.

Furthermore, according to the Centers for Disease Control and Prevention, each year more than 60,000 children are brought to the emergency department (ED) for medication overdoses; OTC medications were implicated in more than 26,000 visits. Ninety percent of ED visits for medication overdoses resulted from unsupervised ingestions of prescription and OTC drugs, with peak incidence in the younger-than-5-year age group.

Most drugs prescribed for children have not been tested in children. Before the US Food and Drug Administration (FDA) initiated a pediatric program (Best Pharmaceuticals for Children

Act of 2002 [amended in 2007]), only about 20% of drugs approved by the FDA were labeled for pediatric use. Currently, about one-third of drugs prescribed to children have been studied for safety and efficacy in pediatric populations. The practice of prescribing drugs for off-label conditions is found in approximately 50% of all physician prescriptions. By necessity, doctors have routinely given drugs to children *off-label,* which means the drug has not been approved for use in children based on the demonstration of safety and efficacy in adequate, well-controlled clinical trials. It does not imply that the drugs are unsafe, improper, or illegal. The Pediatric Research Equity Act of 2003 (amended in 2007) requires pediatric studies and covers drugs and biologics. Under the Pediatric Research Equity Act, the FDA can require pediatric studies of a drug submitted in a new drug application if it determines the product is likely to be used in a substantial number of pediatric patients or if the product would provide a meaningful benefit in the pediatric population over existing treatments. In a systematic review of the frequency of off-label use of antibiotics in clinical pediatric practice, the percentage of off-label antibiotic prescriptions varied from 1% to 94%. Some of the wide variation observed in pediatric patients might be attributed to the heterogeneity among the study populations' ages of children.

Off-label use creates a liability for the physician. The burden of an adverse outcome is on the manufacturer or license holder when there is an on-label use of a medication and an iatrogenic injury is sustained. When the medication is prescribed off-label, legal liability is on the prescriber unless parents and/or guardians are appropriately informed and give their consent.

Differences in pharmacokinetics among infants, children, and adolescents can result in differences in drug efficacy and toxicity. To choose the most important therapeutic, health care professionals must consider a number of factors, including patient characteristics, disease epidemiology, safety profile, patient compliance, and cost-effectiveness (Box 13.1).

Box 13.1. Factors in Choosing Appropriate Therapeutics

Patient Characteristics
- Age
- Medical history
- Allergies
- Use of other medications

Disease Epidemiology
- Epidemiology
- Age-specific factors

Safety Profile
- Therapeutic index
- Black box warning

Patient Compliance
- Taste
- Purpose of treatment
- Storage
- Side effects

Cost-effectiveness
- Drug availability
- Formulary restrictions

Patient Characteristics

Infants and children have different physiological characteristics than adults, including immaturity of metabolic and organ function. Body weight and surface area are considerations in drug dosing for pediatrics. In addition, the therapeutic window for many drugs is smaller for children than adults. Pharmacological factors, including age-based variability in absorption, metabolism, and excretion of drugs in children compared with adults, as well as age-specific contraindications of certain medications, pose special vulnerabilities for children to the adverse effects of overdosing. Conversions of doses from ingredient amounts to volumes for liquids labeled for home use are also problematic.

The patient's medical history plays an important part in the choice of an appropriate therapeutic. Depending on the patient's condition and medical and surgical history, the absorption, metabolism, or usual effectiveness of a therapeutic may be altered. Children with short bowel syndrome can potentially have difficulty absorbing oral medications depending on which portion of the bowel was removed. Children with intellectual disability who are given central nervous system–altering medications can be difficult to monitor for changes in mental status seen with systemic infection. In addition, children with glucose-6-phosphate dehydrogenase deficiency can suffer from drug-induced hemolytic anemia when given certain drugs, such as sulfonamides. Children who are malnourished are at greater risk for drug toxicity because low serum albumin levels decrease the amount of bound drug and result in increased levels of unbound drug in circulation.

Allergies to medications and reactions to prior drugs are important pieces of information to glean from the patient and family. Specific information about symptoms or problems while taking a drug are of great significance because side effects can be mislabeled as drug allergies. *Drug allergies* are reactions that have an immunologic basis. Of the 4 types of immune mechanisms associated with drug allergies, immunoglobulin (IgE)-mediated reactions are of the greatest concern because they can result in anaphylaxis. *Adverse reactions,* such as vomiting, can be idiosyncratic or nonimmune mediated. A *side effect* is an expected but undeniable consequence of taking a medication. Families often attribute any symptoms a patient experienced while taking a medication to a drug allergy. It is, therefore, important to know which side effects are associated with a medication to determine whether an allergy is present. Any medication that has been associated with an allergic reaction (eg, skin eruptions, swelling, urticaria, respiratory difficulty) should not be used without consulting a specialist.

Also important is to consider what other medications the patient is taking. This may influence the drug of choice. Metabolism of 1

drug may influence the metabolism of another. Drug metabolism is divided into 2 types. Phase 1 reactions include oxidation, reduction, and hydrolysis. Phase 2 reactions involve adding subgroups to a drug.

Other drugs can affect reactions during either phase. For example, the enzyme activity of the cytochrome P 450 system involved in oxidation can be induced or inhibited depending on other medications being taken, resulting in an altered rate of metabolism. A common drug used in pediatrics that inhibits the cytochrome P 450 system is erythromycin, while phenobarbital and phenytoin induce the system. Drug interactions are not a contraindication to the use of a therapeutic, but it may be necessary to closely monitor the dose or serum level.

Disease Epidemiology

Etiologies for many common diseases may differ depending on the patient's age group. Some drugs to which the patient's condition may be susceptible are contraindicated in certain patient populations. Treatment duration may also vary depending on the patient's age group (eg, an adult with an uncomplicated urinary tract infection may receive only a 1- to 3-day course of treatment, while a child may receive 7–10 days of treatment because of the high recurrence of infection that has been observed in children given a shorter treatment duration).

Safety Profile

Medications have benefits and risks; these constitute a safety profile. When choosing a medication, the *safety profile* (ie, risks vs benefits) must be evaluated. Some risks may be caused by the duration of treatment, dose, or interactions with other medications. Therapeutic index, which is 1 means of quantifying the risk associated with a specific dose, may be a consideration in medication choice. The *therapeutic index* is the difference between the dose that provides a desired effect and the dose that provides an undesired effect. For example, a medication with a wide therapeutic index is one in which a desired effect is achieved with a dose much lower than that required to produce a toxic effect. In general, a medication with a wide therapeutic index, such as ibuprofen, is considered safer than a medication with a narrow therapeutic index. The higher the morbidity and mortality associated with a condition, the narrower the accepted therapeutic index can be. Food-drug interactions and drug-drug interactions are other risks that can be anticipated. There are also risks that are independent of the dose of the therapeutic, which are called *idiosyncratic effects.* These are unexpected and usually unavoidable risks associated with the medication.

In the United States, a *black box warning,* also known as a *black label warning*, is a type of warning that appears on prescription drugs that may cause serious side effects. A black box warning is the strictest warning that can be put on a label. The name came about from the black border that usually surrounds the text of the warning. Black box warnings mean that medical studies indicate that a drug carries a significant risk of serious or even life-threatening adverse effects. An example of a medication used in pediatrics that has black box warnings is antidepressants. This warning does not prevent the use of the medication but requires the physician and family to evaluate the risks and benefits of its use.

Patient Compliance

Medications and therapeutics are only useful if patients take them as prescribed. Factors that contribute to patient adherence include, but are not limited to, administration convenience and ease of taking the medication, the patient's and family's understanding of the benefits and risks of the medication, and adverse effect profile.

Because children are dependent on their caregivers to administer medications properly, the caregiver must understand why the drug was prescribed, how it should be dispensed, and why it must be taken for a specific length of time. For a medication to achieve its maximal therapeutic usefulness, accurate dosing is important. A staff member should demonstrate how to measure and dispense the medication. The caregiver should then be asked to demonstrate the process. This will make an important difference in adherence to the medication regimen. Having a standardized drug dispensing tool, such as a syringe or marked dosing cup, will potentially improve the ability to give the appropriate medication dose successfully.

In pediatrics, palatability is a major factor in patient adherence. If children do not like the taste or texture of a medication, they will refuse to take it. Physicians who prescribe medications for children should be familiar with the taste and texture and be prepared to find alternatives. Prednisone is a common example of this; it is available as a pill and a suspension. The suspension may taste differently depending on the preparation prescribed. Children often vomit the less-palatable version. Knowing in advance what children will take may prevent future problems associated with noncompliance.

Cost-effectiveness

Cost-effectiveness is defined as outcome per unit cost. *Outcome* is the treatment of the condition or alleviation of the symptoms for which the medication was prescribed. *Cost* includes the price of the medication or treatment as well as the physician's and family's time. Therefore, if a patient is prescribed a medication that is less effective for the child's condition because of cost, it many end up costing more because of the need for additional doctor visits and more medications. In many practice settings, the pharmacy has a set formulary of medication limiting the selection of medications for specific conditions. From the patient side, many families have limited or no health insurance and may have to pay the full cost of a medication. The cost of treating a common condition such as otitis media can differ as much as 10-fold depending on the medication prescribed. Thus, an appropriate drug of choice is influenced by the out-of-pocket cost to the family. The perceived cost-effectiveness of a therapeutic is different for each situation and depends on external factors affecting the physician and family.

Drug Dosing

Compared with the adult population, in which drug doses are based on a standard dose for an individual regardless of age, size, or weight, pediatric medications are usually dosed based on weight or body

surface area. For medication dosing determined by weight, when a child reaches 40 to 50 kg, the dosing is often changed to a standard adult dose. With the increasing prevalence of childhood obesity, many school-age children weigh more than 50 kg, thereby making it important to know the maximum daily dose because calculating milligrams per kilogram can easily exceed this amount. For drugs with narrow therapeutic indexes, such as chemotherapy or immunosuppressive medications, body surface area is used to determine appropriate dosing. Once a therapeutic agent is chosen, an appropriate dosing schedule must be determined. Dosing guidelines can be presented as total dose per 24 hours or an amount per dose. An example for dosing acetaminophen for a 1-year-old is given in Box 13.2.

Medication Errors and Adverse Drug Events

Pediatric patients are at greatest risk for medication errors because of the need to calculate dose based on weight. Between 5% and 27% of all pediatric medication orders result in medical error. Pediatric inpatients incur 3 times more medication errors than adult inpatients. The incidence of adverse drug events in pediatrics is about 2.3%. The most vulnerable populations are patients younger than 2 years; those in intensive care units; those in the ED, especially if they are seriously ill; or those receiving chemotherapy. More than half of these errors occur during the prescribing phase when the medication dose is calculated. Dosing error checking is complicated by the fact that children's weights vary from as little as 500 g to much more than 100 kg. Therefore, a dose range for a medication may be very large. The second most common causes of error in pediatric prescriptions is missing information and illegibility. In 2001, the Institute for Safe Medication Practices published guidelines to decrease pediatric medication errors. Their recommendations included computerized physician order entry, bar coding technology, unit dose dispensing systems, and educational programs for all health care professionals. There is no literature to support these recommendations. There have been multiple studies trying to identify definitive interventions, but, to date, no studies have been able to elucidate effective solutions.

The American Recovery and Reinvestment Act of 2009 provided much-needed momentum toward widespread electronic health records, which include e-prescribing. Systems that have computerized physician order entry or e-prescribing can reduce medication errors by having alerts for inappropriate dosing, improved legibility, warnings for drug interactions, and just-in-time information on the most appropriate drug choice. Not all errors will be rectified by e-prescribing; examples of errors that elude decision-support programs include inappropriate selection of medication for the condition being treated and failure to recognize a change in patient status.

Box 13.2. Dosing Example: Acetaminophen

A 1-year-old has a fever, and the family wants to know how much acetaminophen to give her. She weighs 11.2 kg (24.7 lb). The recommended dose of acetaminophen is 10 to 15 mg/kg every 4 to 6 hours. Acetaminophen is sold as a suspension with the concentration of 160 mg/5 mL.

1. Determine the amount of medication needed by multiplying the weight of the child by the recommended dose.

$$11.2\ \text{kg} \times 10\ \text{mg/kg} = 112\ \text{mg acetaminophen}$$

2. Determine the volume of medication based on the concentration of acetaminophen to be used.

Dosing volume = (amount of medication) ÷ (concentration of medication)

Suspension

$$\text{Dosing volume} = 112\ \text{mg} \div 160\ \text{mg/5 mL}$$
$$= (112 \times 5)/160$$
$$= 3.5\ \text{mL}$$

This family can be instructed to give the 1-year-old 3.5 mL of the suspension of acetaminophen orally every 4 to 6 hours as needed for fever.

CASE RESOLUTION

After obtaining the history and performing a physical examination, the pediatrician determines that the patient has acute otitis media. Depending on the age of the child and the severity of symptoms, American Academy of Pediatrics clinical practice guidelines suggest a stratified approach to therapeutics. For infants and children between 6 and 24 months of age, pediatricians can treat with antibiotics if the diagnosis is certain or observe the patient without antibiotics if the patient is otherwise healthy. In this case, the pediatrician discusses the options with the family and, because of the severity of pain and previous ear infections, chooses to treat the infection. The antibiotic of choice for treatment of otitis media is amoxicillin at a dose of 80 to 90 mg/kg/day. The mother states that her daughter had hives with amoxicillin, a type 1 hypersensitivity. Other antibiotic choices would include cefdinir 14 mg/kg/day in 1 to 2 doses per day. Treatment of pain is essential with otitis media. The patient can take oral acetaminophen or ibuprofen.

The mother raises a concern about her daughter's cough and runny nose and would like to use an OTC cough medication. The US FDA does not recommend use of cough preparations in this age group. Educating the mother about conservative therapies, including nasal suctioning, humidification, and nasal saline, to treat her daughter's respiratory symptoms is more appropriate.

If the patient were not allergic to amoxicillin, it would have been the drug of choice. It is inexpensive, has a narrow microbiological spectrum, and is palatable. Amoxicillin does require refrigeration, which would be of concern if the family were traveling. While this case illustrates several obvious constraints, it is important to emphasize that choosing the appropriate medication is dependent on the intrinsic needs of the patient and extrinsic factors that can affect adherence and, ultimately, the effectiveness of treatment.

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CHAPTER 14

Pediatric Pain and Symptom Management

Kevin Madden, MD, and Richard Goldstein, MD, FAAP

CASE STUDY

You are caring for a Kayla, a 10-year-old girl with stage 4 neuroblastoma who is at home receiving palliative care. Her tumor is refractory. She receives oral chemotherapy and transfusions as an outpatient to offset the bone marrow depletion caused by her tumor. Pain from her metastases is becoming increasingly problematic, especially in her chest wall and right femur. Her spine is also involved, but she does not experience weakness. Although fatigued, she derives great pleasure from attending school and being surrounded by friends and family members, playing as she is able. She hates the hospital and her parents have chosen to avoid it, intending to keep her comfortable at home until she dies. You have remained closely involved throughout her illness and would like to help with the management of her symptoms.

Questions

1. What is the approach to pain management in children?
2. How does the physician assess the level of pain in children?
3. What is meant by adjuvant therapy?
4. What are nonpain symptoms that can cause distress?
5. What is the management of nonpain symptoms?

Ill or injured children experience distressing physical symptoms, particularly in the case of illness or injury that is chronic or life-limiting. The appropriate management of such symptoms is fundamental to minimizing discomfort and optimizing quality of life. Pain can not only diminish a child's physical well-being but also can affect psychological, social, and spiritual health. Children experiencing poorly controlled pain will withdraw interpersonally and be unable to engage in the activities that make their life, however limited, meaningful. Similarly, a child troubled by nausea will experience distress from the symptom while also losing the simple pleasure of eating and its accompanying comforts. Symptom management improves the lives of children who are medically fragile.

Parents or caregivers of children who are seriously ill worry most about their child's symptoms not being satisfactorily controlled. Studies of dying children have noted that distressing symptoms often go untreated. Research investigating the symptoms and experience of children dying from cancer found that most of the children experienced fatigue, pain, dyspnea, anorexia, nausea and vomiting, and constipation in the last month of their lives (Figure 14.1). Similar findings have since been noted in other populations. Children with neurologic impairment are particularly at risk because of their limited verbal abilities and atypical responses to pain. Symptom management of seriously ill children has been improved significantly since early studies. As more children with chronic and serious illnesses are cared for and sometimes die at home, the management of their illnesses will increasingly involve their primary care pediatrician.

This chapter reviews the basic medical approaches to pain and symptom management in children, particularly those with serious illnesses. In addition to pain, approaches to nausea, anorexia, fatigue, secretions, and delirium are presented. The focus is on the medical management issues a primary care pediatrician may attempt to manage in the community setting. When the primary care pediatrician is insufficiently familiar with such treatment, consultation with pain or palliative care specialists is appropriate.

Pain

Pain is an integrated biophysical and "existential" construct. It involves complex mechanisms of nociception modulated by biochemical factors, neuroplasticity, genetic and familial factors, and an individual's past experience with painful events. Each child experiences pain in a unique way and quickly develops learned behaviors related to it. As such, no simple correlation exists between the objective degree of injury and the experience of pain. More accurately, physical, psychological, interpersonal, and existential factors all contribute in important ways to the experience of pain. A comprehensive approach to pain addresses all these elements.

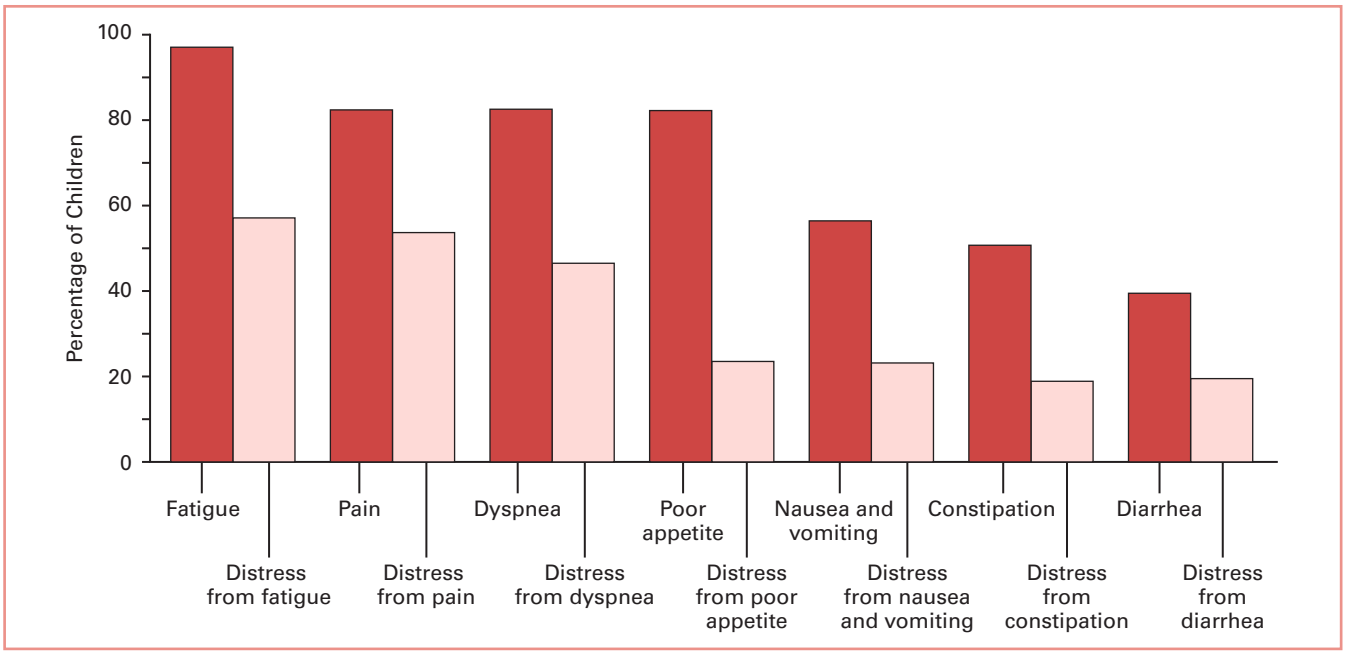

Figure 14.1. The presence and degree of distress from specific symptoms in the last month of life.
Adapted with permission from Wolfe J, Grier HE, Klar N, et al. Symptoms and distress at the end of life in children with cancer. *N Engl J Med.* 2000;342[5]:326–333.

Assessment

The 2 basic types of pain are nociceptive and neuropathic. An understanding of the presentation of each type can help differentiate the source of pain in children. *Nociceptive pain* is the activation of peripheral nerve receptors when noxious stimuli cause tissue damage, and its intensity is related in part to the location and the amount of damage. *Somatic pain* refers to nociceptive pain from musculoskeletal, bony, or superficial sources (eg, skin, mucosa). Deep somatic pain tends to be localized and concentrated and is described as stabbing, aching, or throbbing (eg, bone pain is deep and aching). Superficial somatic pain is sharper and can be burning or pricking. The source of nociceptive pain can also be visceral. *Visceral pain* is usually poorly localized; can be described as cramping, gnawing, or pressure; and may follow daily patterns of varying intensity.

Neuropathic pain is caused by injury or dysfunction of the central nervous system (CNS) or peripheral nerves. It can be described as burning, tingling, shooting, or scalding. Its presence points to neuropathies, CNS insult, or evolving damage to the nervous system. Understanding whether the source of pain is somatic, visceral, or neuropathic helps guide treatment decisions.

Pain should be a part of the medical evaluation of every child. Pain is phenomenological and thus, although its existence is "real" and "objective," it can be experienced and described only by the affected person. Fundamentally, the patient's report of the presence or severity of pain is the key to the assessment. In children, especially children with developmental issues, objective assessment tools may be useful to identify the presence of pain and quantify its severity. In most patients these scales are also helpful in understanding the symptom of pain over time.

Standardized pain scales are used to assess the intensity of pain. Analog pain scales, which generally score intensity on a scale of 1 to 10, have some reliability when used in the same patient over time (Figure 14.2). Younger children may have difficulty with the concept of quantity or the meaning of greater intensity. An important modification of the analog scale for children with impaired communication skills or cognition is the *Individualized Numeric Rating Scale*, on which parental or caregiver observations of their child's facial expression, body movements, activity and interaction, crying, and ability to be consoled as they experience worsening pain are used to label the points of the scale.

For children older than 3 years, the *Wong-Baker FACES Pain Rating Scale* (Figure 14.3) is often used. After showing children the faces, they are instructed that each face is for a person who has no pain (no hurt), some pain, or a lot of pain. The child is then asked to choose the face that best describes how the child is feeling. More comprehensive pain assessment tools are available that also assess function and mood, but they are less widely used. The perspective of parents or caregivers and others familiar with the child is crucial to any assessment of a child's pain.

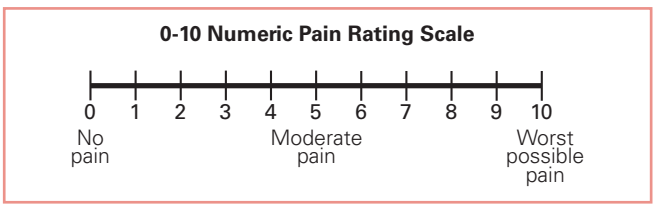

Figure 14.2. Visual analog pain scale.
Reprinted with permission from McCaffery M, Pasero C. *Pain: Clinical Manual.* 2nd ed. St Louis, MO: Mosby; 1999.

Figure 14.3. Wong-Baker FACES Pain Rating Scale.
Reprinted with permission from Wong-Baker FACES Foundation [2014]. Accessed August 17, 2019, www.WongBakerFACES.org.

The child in pain must be relieved of it; however, it is advantageous to make a strong effort to understand the source of the pain and manage conditions amenable to nonpain medication. For example, chest pain may be caused by candidal esophagitis or abdominal pain resulting from constipation. Thinking clearly about the etiology of pain rather than simply providing analgesic agents in a reflexive manner has the benefits of preserving alertness, sparing side effects, and sustaining the least impaired quality of life. Pain can be eliminated by eliminating the underlying condition responsible for it. The optimal management of pain also includes addressing psychosocial and spiritual distress and making efforts to enhance a child's function as part of an integrated approach to pain-related distress.

Medical Management

Opioids are the pharmacologic mainstay of pain management. Familiarity with the basic principles of treatment with these agents is fundamental to care for the child with serious acute and life-limiting illness. In cases of complex pain or those involving daunting polypharmacy, it may be best to seek guidance from pain or palliative care specialists. Additionally, certain medications (ie, methadone, selective norepinephrine reuptake inhibitors) or invasive approaches (ie, intrathecal pumps, regional blocks, surgical or radiotherapeutic approaches to pain control), or the management of chronic pain, particularly in adolescents, should involve consultation with or referral to pain and palliative care specialists.

The use of opioids in children since approximately 1990 roughly parallels wider trends observed in their use in adults. The 1990s and early 2000s saw a dramatic increase in the number of opioid prescriptions in the United States, motivated by the assessment that pain in seriously ill children was being undertreated. Changing prescribing practices also heralded a new public health crisis, the opioid-overdose epidemic. Currently, opioid overdoses are the leading cause of death of Americans younger than 50 years. The philosophical pendulum is now swinging back towards a more scrutinized prescribing environment. Some commercial pharmacies limit new prescriptions of opioids for noncancer pain to a 7- to 10-day supply, and many state medical boards now require physicians to review prescription drug monitoring program databases on a routine basis. Parents have responded to this widely publicized phenomenon with renewed caution about opioids, while seeking the benefits of appropriate use. Proposing an opioid for a child now demands considerable investment by the physician to provide a comprehensive pain plan that highlights consistent reassessment of the need for an opioid, directly addresses the specter of dependency before initiation of an opioid, and reassurance that the child's best interest will always be the focus of treatment.

Pain must be understood as a multidimensional symptom with a meaning for the individual that influences the experience of it, worthy of its own attention. In the context of "total pain," other etiologies of pain should be considered, assessed, and managed, especially when a child's or parent's/caregiver's report of pain intensity seems incongruous with the amount of opioid provided. *Total pain* conceives of pain as having 4 interrelated domains: physical, psychological, social, and spiritual. The use of opioids may unintentionally alleviate psychological, social, and spiritual pain as the limbic system also possesses mu receptors, but it cannot substitute for attention to all the elements of pain. Activation of these specific mu receptors upregulate mood, which can easily become intertwined and confused with relief of physical pain.

Dose escalation should proceed until the pain is controlled, provided that side effects are tolerable. Opioids have no maximum or "ceiling" dose. The child on long-term opioid treatment often receives surprisingly high doses yet, provided the treatment is successful in controlling pain, is comfortable and functional. Generally, infants younger than 6 months should be started at one-third the general pediatric dose. Anticipated side effects of opioids include constipation, pruritus, and nausea and vomiting. The pruritus and nausea and vomiting are usually short-lived, disappearing in a week, but constipation persists. All patients on scheduled opioids should also receive scheduled doses of stool softeners and stimulant laxatives.

Parents or caregivers and some physicians may overestimate the benefit of distraction in pain management. Distraction is best thought of as an assessment tool and may be an adjunct to but not a treatment for pain. If a child can be substantially distracted from the pain for a significant period, the pain need not be managed with medication. If the child's distress is apparent despite the distraction, however, pharmacologic intervention for the pain is necessary. What must be avoided is a distressed child engaging in the distraction to please adults while the pain goes unabated. Similarly, the use of placebos has no place in the treatment of pain.

The World Health Organization 2-step approach to pharmacologic management of pain is the most important guide to pain management in children. It presents a stepwise and additive approach to "capture" a child's pain as well as to augment the pharmacologic treatment of pain. The model is premised on using a 2-step strategy, dosing at regular intervals, using the appropriate route of administration, and individualizing treatment to the particular child.

The child with mild pain who has not received any analgesic medication is managed with oral analgesics, such as acetaminophen and ibuprofen (step 1). In certain cases, intravenous acetaminophen or ketorolac tromethamine may be used. Adjuvants may be added if appropriate. Acetaminophen can be given orally or rectally. Compounded ibuprofen can be given rectally. The topical application of these agents in ketoprofen cream or aspirin cream may also

be of benefit. Rarely, a role may exist for a cyclooxygenase-2 inhibitor. All nonsteroidal anti-inflammatory drugs have ceiling doses and gastrointestinal toxicities. With the exception of acetaminophen and celecoxib, all affect platelet function and hemostasis.

Adjuvants are non-analgesic drugs that are helpful in the management of a child's pain. For example, anxiety experienced by a child who is medically fragile may potentiate the child's pain and distress, even at step 1. A benzodiazepine may be helpful in such cases, but it should be prescribed with an awareness of other medications. An alternative to benzodiazepines for anxiety is the antipsychotic agent haloperidol. At very low doses it provides an anxiolytic effect without sedation or the synergism with opioids that can result in respiratory depression. A lidocaine patch can help with some somatic pain. Certain forms of mild to moderate pain (ie, neuropathic pain) may be adequately managed with gabapentin or pregabalin, minimizing the use of opioids.

Step 2 addresses children with moderate to severe pain and involves the addition of opioids to the treatment plan (Table 14.1). "Weak opioids" (eg, codeine, tramadol hydrochloride) are no longer recommended. Research has shown that codeine may be a weaker analgesic than a standard dose of many nonsteroidal anti-inflammatory drugs, and it has a ceiling effect. The oral bioavailability of codeine is widely unpredictable, at 15% to 80%. Most importantly, codeine is a prodrug that must be metabolized by the liver into morphine. This is problematic because it is estimated that 35% of children do not metabolize codeine in the anticipated manner, resulting in great uncertainties in a calculated effect. The use of tramadol hydrochloride is only weakly recommended because of concerns

Table 14.1. Essential Pharmacopeia for Symptom Management in Pain and Palliative Care

Symptom	*Agent*	*Initial Oral Dosing*	*Initial IV Dosing*	*Available Formulations*
Pain	Hydromorphone	0.04–0.06 mg/kg every 3–4 hours (max, 2 mg/dose)	0.015 mg/kg every 2–3 hours (max, 0.6 mg/dose)	Immediate release: tablet, liquid Extended release: tablet IV
	Morphine	0.2–0.3 mg/kg every 3–4 hours (max, 15 mg/dose)	0.05–0.1 mg/kg every 2–3 hours (max, 5 mg/dose)	Immediate release: tablet, liquid Extended release: capsule, tablet IV
	Oxycodone	0.1–0.2 mg/kg every 3–4 hours (max, 10 mg/dose)	N/A	Immediate release: tablet, liquid
Anorexia	Cyproheptadine hydrochloride	0.25 mg/kg/day in 2–3 divided doses (max, 12 mg/day)	N/A	Tablet
	Megestrol acetate	10 mg/kg/day in 1–4 divided doses[a]	N/A	Tablet, liquid
Delirium	Haloperidol	0.01–0.02 mg/kg every 4–6 hours (max, 0.5–1 mg/dose)	0.01–0.02 mg/kg every 4–6 hours (max, 0.5–1 mg/dose)	Tablet, liquid, IV
	Olanzapine	1.25–5 mg every 4–6 hours	N/A	Tablet, oral disintegrating tablet
	Quetiapine fumarate	12.5–50 mg every 6–8 hours	N/A	Tablet
Dyspnea	Any opioid	33%–50% of opioid dose for pain	33%–50% of opioid dose for pain	Any formulation
Dystonia	Baclofen	2.5–5 mg every 8 hours	N/A	Tablet, liquid
	Diazepam	0.5 mg/kg/dose every 6 hours as needed	0.5 mg/kg/dose every 6 hours as needed	Tablet, IV, rectal gel[b]
Fatigue	Methylphenidate hydrochloride	2.5–5 mg daily or twice a day	N/A	Tablet, transdermal patch[c]
Nausea	Ondansetron hydrochloride	0.15 mg/kg/dose every 8 hours (max, 8 mg/dose)	0.15 mg/kg/dose every 8 hours (max, 8 mg/dose)	Tablet, oral disintegrating tablet, liquid, IV
	Metoclopramide hydrochloride	0.1–0.2 mg/kg every 6 hours (max, 5 mg/dose)	0.1–0.2 mg/kg every 6 hours (max, 5 mg/dose)	Tablet, liquid, IV
Respiratory secretions	Atropine 1% ophthalmic drops	1 drop every 2 hours as needed	N/A	Liquid
	Glycopyrrolate	0.04–0.05 mg/kg every 4 hours	0.004–0.005 mg/kg every 4 hours	Tablet, liquid, IV

Abbreviations: IV, intravenous; max, maximum; N/A, not applicable.

[a] Only for children >10 years of age.

[b] Dose equivalent to oral or IV dose.

[c] Dose equivalent to oral dose.

about risks for seizures and hyperserotonergic symptoms with its use.

When pain persists or worsens, morphine, hydromorphone, and oxycodone are recommended initial choices. Doses are escalated until pain is controlled, using the least invasive form of administration necessary. This step may involve the addition of controlled-release preparations of opioid or methadone, while using shorter-acting agents for breakthrough pain. To calculate the as-needed dose for breakthrough pain, a general rule is that the as-needed dose is 10% to 15% of the 24-hour total opioid dose or its equivalent, given orally every 3 to 4 hours.

An in-depth discussion of methadone and fentanyl citrate exceeds the scope of this chapter, but it is worth making several points about them. Neither has active metabolites, making them important options for patients with renal failure in whom accumulated metabolites from other opioid agents can cause myoclonus, confusion, or hyperalgesia. Fentanyl citrate, a potent analgesic, is available in a transdermal patch, which is an important nonintravenous, non-oral option for children having difficulty swallowing. The child must have adequate body fat, because the drug is deposited across the rate-limiting membrane into fat reservoirs and is absorbed from that reservoir into the child's bloodstream. Methadone has some distinct analgesic advantages. It is inexpensive, its half-life allows for more convenient twice-a-day or 3-times-a-day dosing, and it is especially helpful in managing neuropathic pain. It is complicated to dose, however, and its long and variable half-life make it a more complicated choice for those not familiar with its use.

The management of moderate and severe pain over time can result in the development of difficult unintended effects, including sedation, nausea and vomiting, pruritus, and urinary retention. At high doses or when metabolites accumulate, patients may develop delirium, myoclonus, or hyperesthesia. Opioid rotation can be quite helpful in these situations. This method involves converting 1 form of opioid to an equivalently analgesic dose of another.

Rotation of the opioid agent (ie, using a different opioid) holds the promise of maintaining analgesia with lesser amounts of the newly introduced drug and eliminating side effects. *Tolerance* is the term used to describe the need over time for increased amounts of a specific opioid to achieve the desired analgesic effect. Although opioids lack a ceiling dose, higher doses may have an accompanying increase in adverse effects (ie, the emergence of the intolerable side effects noted previously, the accumulation of toxic metabolites, or high cost resulting from the required amounts of the drug). Because of multiple mu opioid peptide receptors as well as different selectivity of opioids for specific mu opioid peptides, the cross-tolerance from 1 opioid to another is not complete. An equianalgesic dose of another opioid will require less of the medication and achieve a more favorable balance between analgesia and side effects. See Box 14.1 for an example of opioid conversion.

Physicians lacking experience in pain management may be concerned about the difficulty of addressing uncontrolled pain. Because expert and effective management is a critical skill in the care of seriously ill children, especially those facing the end of life, the primary care physician may choose to consult with palliative care or pain treatment specialists to ensure that the child's needs are adequately addressed. Alternatively, hospice medical directors can provide palliative care consultations if hospital-based teams are not available.

The optimum of opioids is impacted by factors related to both patients and physicians. Foremost is the concern about respiratory depression. The risk of respiratory depression while using an accepted escalation rationale is quite small, however. Patients may fall asleep when their pain is "captured," but this generally is the result of exhaustion related to the previously unrelieved pain. Even in mild to moderate pain, patients do not notice a change in dose increase when they are less than 25% above baseline. In cases of moderate to severe pain, a dose escalation of 50% to 100% is appropriate. For acute pain crises, protocols exist that allow physicians to safely mitigate pain, but consultation with pediatric palliative care or pediatric pain specialists may help the less comfortable physician act more decisively. It is nonetheless important to recognize that the

Box 14.1. Opioid Conversion Example

Kayla is receiving 30 mg of long-acting oxycodone every 8 hours and 15 mg of immediate release oral morphine every 4 hours as needed for breakthrough pain. She receives approximately 4 doses of as-needed morphine per day. She can no longer walk and finds it progressively more difficult to swallow pills. The decision is made to rotate (ie, change) her opioid to intravenous (IV) hydromorphone.

Steps in opioid conversion

1. Calculate the total 24-hour dose of each opioid
   a. 30 mg oxycodone × 3 = 90 mg oxycodone
   b. 15 mg morphine × 4 = 60 mg morphine
2. Convert 24-hour total of each opioid to the morphine equivalent daily dose (MEDD), always expressed as oral mg of morphine
   a. 90 mg oxycodone = 135 mg oral morphine (oxycodone is ≈1.5 times more potent than oral morphine)
   b. 60 mg oral morphine = 60 mg oral morphine
   c. MEDD = 135 + 60 = 195 mg oral morphine
3. Convert MEDD to new opioid (use opioid equivalency table [Table 14.2])
   a. 195 mg / 20 (IV hydromorphone is ≈20 times as potent as oral morphine) = 9.75 mg IV hydromorphone/day
4. Dose reduce the MEDD by 33%-50% to account for incomplete cross-tolerance
   a. 9.75 mg × 0.66 = 6.5 mg/day
      i. 6.5 mg / 24 hours = 0.27 mg/hour
5. Determine an as-needed dose, that is, 10%-20% of the 24-hour opioid dose
   a. 6.5 × 0.1 = 0.65 mg IV every 2 hours as needed for breakthrough pain ***OR***
   b. 6.5 × 0.2 = 1.3 mg IV every 2 hours as needed for breakthrough pain

For Kayla

IV hydromorphone infusion of 0.27 mg/hour with IV hydromorphone 0.65-1.3 mg IV every 2 hours as needed for breakthrough pain

Table 14.2. Opioid Equivalency

Drug	*Oral Route*	*Parenteral Route*	*Conversion Ratio to Oral Morphine*	*Equianalgesic Dose of Oral Morphine*
Morphine sulfate	30 mg	10 mg of parenteral morphine	Parenteral morphine is 3 times as potent as oral morphine.	30 mg
Oxycodone	20 mg	N/A	Oral oxycodone is approximately 1.5 times more potent than oral morphine.	30 mg
Hydrocodone	20 mg	N/A	Oral hydrocodone is approximately 1.5 times more potent than oral morphine.	30 mg
Hydromorphone	7 mg	1.5 mg of parenteral hydromorphone	Oral hydromorphone is approximately 4–7 times as potent as oral morphine. Parenteral hydromorphone is 20 times as potent as oral morphine.	30 mg
Fentanyl citrate	N/A	15 mcg/hour	Transdermal fentanyl citrate is approximately 80 times as potent as morphine.[a]	30 mg

Abbreviation: N/A, not applicable.

[a] This is based on studies converting from morphine to fentanyl citrate. Currently, there are no empirical studies converting fentanyl citrate to morphine.

Adapted with permission from Periyakoil VJ. Opioid conversion equivalency table. Palliative.stanford.edu website. https://palliative.stanford.edu/opioid-conversion/equivalency-table/. Accessed July 3, 2019.

co-administration of an opioid and benzodiazepine increases the risk for apnea and respiratory insufficiency. When alveolar pCO_2 (partial pressure of carbon dioxide) reaches 60 mm Hg, normal alveolar minute ventilation increases almost 10-fold from baseline, yet the compensatory increase in alveolar minute ventilation is largely absent when an opioid (eg, fentanyl citrate) is co-administered with a benzodiazepine (eg, lorazepam). In the rare situation in which naloxone hydrochloride is required to reverse a worrisome respiratory effect, the experienced physician can slowly titrate it to reverse respiratory insufficiency and preserve the analgesic effect of the opioid rather than administer the entire dose at once. Physicians may also be unfamiliar with appropriate dosing, may not view pain control as a priority of care, or may be worried about difficulties ensuring follow-up and ongoing assessment. Families, for their part, may believe that pain is an inevitable part of the child's disease, may worry about the "symbolism" of starting a morphine drip as a hastening of death, or may worry about addiction or the stigma of having their child on such medications. Cultural and religious factors may also elicit reluctance. Such concerns should be addressed directly. The greatest concern should be to minimize any distress caused by inadequately managed pain.

The management of neuropathic pain presents a considerable challenge. The source of neuropathic pain is the insult or dysfunction of the CNS, peripheral nervous system, or autonomic nervous system. Pediatric patients may experience this pain as the result of degenerative CNS processes or injury as well as the result of treatment-related injuries to the nervous system from drug toxicities, radiation therapy, surgery, or physical compression of a nerve by a tumor. Infection may also cause neuralgia. Children describe neuropathic pain as jolts of burning, stabbing, or shooting; the pain seems to worsen at night and, compared with nociceptive pain, usually has an abrupt, unpredictable onset and a shorter duration, sometimes lasting only minutes and thereby making it difficult to manage exacerbations of pain. It also causes allodynia, dysesthesia, and hyperalgesia. The results of various approaches to the management of neuropathic pain are mixed, and a multimodal approach, including an emphasis on physical therapy and more than 1 therapeutic agent, is recommended. Adjuvant medications are offered as first-line therapy in children, with gabapentin beginning at 10 mg/kg/day divided 3 times a day and titrating upward to doses as high as 60 mg/kg/day. Emerging evidence in adults indicates that the serotonin–norepinephrine reuptake inhibitor duloxetine hydrochloride may provide better neuropathic pain control than gabapentin, with fewer side effects (eg, fatigue, excessive somnolence). Strong opioids, including methadone hydrochloride, may be included in an appropriate regimen. Tricyclic antidepressants tend to be used less for children in the management of neuropathic pain because of concerns of arrhythmia risk.

Dystonia and neuroirritability, although not properly neuropathic pain, present similar challenges in children with neurodegenerative conditions. Generalized dystonia is a condition in which sustained, erratic, painful muscle contractions occur, causing twisting and repetitive movements or abnormal postures. *Neuroirritability* is a term used to describe the difficulty in settling and persistent crying seen in some children who are cognitively impaired with metabolic and neurodegenerative conditions. These symptoms are distressing and often occur in children whose impairments make assessment of their experience difficult. Benzodiazepines, typically diazepam, are the first-line therapy for dystonia (see Table 14.1). Trihexyphenidyl hydrochloride is also commonly considered, as are valproate sodium, baclofen, carbamazepine, and tetrabenazine. In severe, intractable cases the implantation of deep brain stimulators is increasingly considered, although the empiric basis for that decision remains under study. Anticonvulsant agents are the mainstay in the management

of neuroirritability. Phenobarbital is often the first medication tried. The management of these conditions is generally determined in consultation with a child neurologist.

Management of Nonpain Symptoms

Agents used in the management of nonpain symptoms are listed in Table 14.1.

Dyspnea

Many similarities exist between the management of severe dyspnea and severe pain. Dyspnea is caused by increased work of breathing, hypoxia, and hypercapnia and the driving desire of the brain to relieve these conditions. Experientially, it may cause a feeling similar to that of being underwater too long and needing to surface. Like pain, dyspnea has a physical basis; however, the distress is potentiated by psychological, interpersonal, and existential aspects. After oxygen, opioids are the treatment of choice, and they are dosed at one-third the dose for pain management. The inexperienced physician may be concerned about exacerbating the patient's dyspnea by causing respiratory depression, but strong evidence exists for the effectiveness and safety of low-dose opioids: At appropriate doses, opioids reduce breathlessness and provide benefit to patients with limited risk of respiratory depression. Because of the anxious state dyspnea often causes and because anxiety worsens dyspnea, an appropriate dose of a benzodiazepine may also be helpful, although never as the principal medication. Environmental measures, such as the breeze from an electric fan on the patient's face or decluttering the room, also can bring relief. It is important to recognize that dyspnea is a subjective sensation and that although the patient may report improved dyspnea, tachypnea, increased work of breathing, and retractions may persist. The goal of managing dyspnea is making the patient feel better, not necessarily look better.

Nausea and Vomiting

Nausea and vomiting are common symptoms in children with complex illnesses and those facing the end of life and are significant sources of distress and discomfort. These conditions can have different etiologies, principally gastrointestinal, CNS, or treatment related. The child with neurologic impairment can experience retching, and many of the medications used in the management of the impairment have nausea among their side effects. Children are especially vulnerable to *anticipatory nausea*, a conditioned behavioral response in anticipation of a medication or procedure that has caused nausea and vomiting in the past. Anorexia can be a symptom of low-grade nausea. An approach to nausea and vomiting based on an understanding of the cause of the symptom exacerbation and of the symptom mechanism can prove valuable. A careful history and physical examination, with special attention to medications and procedures, is crucial.

Although a patient's presentation may be complex, determination of appropriate management may be simplified by understanding the 4 pathways to nausea and vomiting. The vomiting center, which lies in the brain stem, receives input from the chemoreceptor trigger zone (CTZ), the cerebral cortex, peripheral pathways in the gastrointestinal tract, and the vestibular system. The CTZ responds to toxins and medications in blood and spinal fluid; the cerebral cortex responds to sensory input, anxiety, meningeal irritation, and elevated intracranial pressure; peripheral pathways are stimulated by mechanical stretch in intestinal obstruction and by mucosal injury; and the vestibular system is affected by motion and labyrinth disorders. Each pathway involves different neuroreceptors for targeting in mechanism-based therapy.

The CTZ can be suppressed by the blockage of dopamine D_2 receptors with haloperidol, olanzapine, prochlorperazine, chlorpromazine, or metoclopramide hydrochloride. Peripheral pathways can be addressed by identifying the underlying cause and with the blockage of 5-hydroxytryptamine, serotonin 3 receptors by ondansetron hydrochloride. The cortex can be addressed with anxiolytics, attention to sensory stimuli (eg, smells, tastes), and, in cases of elevated intracranial pressure, high-dose steroids. Dronabinol may also be helpful. The vestibular system is managed by blocking muscarinic acetylcholine and histamine receptors with scopolamine, hyoscyamine, and diphenhydramine. Although promethazine hydrochloride is useful in adults, it should be avoided in children because of its implication in sudden death in some individuals in that population.

The symptoms of nausea and vomiting often involve multiple pathways. For instance, opioid-induced nausea and vomiting may be the result of constipation or gastroparesis, stimulation of the CTZ, or sensitization of the labyrinth. Choices must be made about how to approach the possible causes in a stepwise manner. The literature suggests that mechanism-based therapy is more effective, uses a systematic approach that identifies all possible contributors, and encourages the management of underlying causes. It uses medication in a targeted manner, thereby reducing the risk of untoward effects and oversedation. Finally, the risk of extrapyramidal side effects is greater in children than adults, and when using high doses of metoclopramide hydrochloride or the phenothiazines, premedication with diphenhydramine is recommended.

Anorexia

Anorexia is an anticipated symptom at the end of life. Some parents and caregivers have great difficulty with this symptom and can feel overwhelmed by the loss of a concrete expression of their nurturing. They want their child to eat to be better able to fight the illness. Food preparation and feeding the child is something concrete a parent or caregiver can do for their child. Children who are dying want to please their parents or caregivers as much as healthy children if not more so. It is important to acknowledge the feelings behind the desire of parents and caregivers for their child to eat. Small portions of the child's favorite foods or new favorites the child requests may be comforting to all.

Times exist earlier in an illness when it may be appropriate to improve appetite. Cyproheptadine hydrochloride has a long history of safe use in children and has been shown to be helpful in some cases. Megestrol acetate has been shown to be effective in increasing weight but not muscle mass and may be considered in children over the age of 10 years, although use in children has not received US Food

and Drug Administration approval. Although cannabinoids stimulate appetite, they have not been demonstrated to increase weight. The use of steroids, which are likely to improve appetite, often comes at an unacceptable cost of irritability and immunosuppression.

One other consideration related to feeding is whether children are "starving" when they no longer have the desire to eat, a commonly expressed concern of parents and caregivers. Research comparing the anorexia-cachexia syndrome with starvation shows 2 quite different metabolic states. Differences in energy expenditure, protein synthesis and proteolysis, glucose metabolism, and hormonal levels reinforce the belief that anorexia-cachexia is a hypermetabolic state, whereas starvation in the healthy individual is an effort by the body to conserve itself. An understanding of this difference enables the physician to explain to parents or caregivers how the disease is robbing the child's energy and that it is not the fault of their efforts or the lack of food. In fact, research on adults dying of advanced cancer found that even the patients who ate the most lost weight.

Respiratory Secretions

Respiratory secretions are a common symptom in children who are seriously ill. Children with neuromuscular diseases and neurologic impairment can have difficulty managing secretions. The presence of a tracheostomy can further complicate matters. The use of suction- and cough-assist machines is important, particularly in the setting of acute respiratory illnesses that cause increased secretions. In children at this stage of illness, drying agents (eg, glycopyrrolate, atropine, scopolamine, hyoscyamine) are sometimes helpful, but they may increase the risk of acute obstruction by thickening secretions and causing mucus plugging.

Terminal secretions (the "death rattle") are understandably quite distressing to parents and caregivers, although the child is not typically bothered by them. These secretions are not relieved by suctioning, and they often worsen because the stimulus of the suction catheter can reflexively increase saliva and mucosal secretions; however, the obstruction and noise of secretions often respond to repositioning of the head and neck. Drying agents are usually prescribed in this setting. Switching between agents lacks much advantage if the effect is not substantial, although more than 1 agent should be tried. Glycopyrrolate is the only such agent that does not cross the blood-brain barrier and thus, it is the least likely to cause CNS effects such as confusion, agitation, and delirium.

Fatigue

Fatigue is a highly prevalent symptom at the end of life. In a study of children with terminal cancer, 96% were found to have experienced fatigue in their last month. This symptom is especially disheartening, because fatigued children may have the desire to do things that provide a quality of life but not feel up to the task. Fatigue may be caused by illness, treatments, stress, isolation, poor sleep hygiene and circadian disorientation, mood, or the lack of pleasure or activity. The sedative effects of some medications certainly contribute. Sleep, exercise, nutrition, anemia treatment, increased interactions, and activity all have been shown to have a beneficial effect in decreasing fatigue. Medical therapy with methylphenidate hydrochloride or modafinil may be helpful, dosed at lower amounts than typically prescribed for attention-deficit/hyperactivity disorder.

Delirium

Delirium is most simply conceived as organic brain dysfunction and is common at the end of life. The diagnosis of delirium can be challenging, especially in children, because of the vast developmental range. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, diagnostic criteria are a disturbance in attention, a change in cognition, and whose onset is acute and whose intensity fluctuates during the day. Delirium can manifest as hyperactivity (ie, agitated, combative), hypoactivity (ie, withdrawn, appear to be sleeping), and mixed (ie, hyperactive and hypoactive). Given these challenges, use of a validated, behavioral-observational tool is encouraged, such as the *Cornell Assessment of Pediatric Delirium*. It is important to counsel families that delirium can cause disinhibited behavior, commonly seen as increased pain expression. Delirium must be aggressively managed with haloperidol, olanzapine, or quetiapine fumarate to also achieve good pain control.

CASE RESOLUTION

Kayla lived for 4 more months, was never again admitted to the hospital, and until her last days, remained engaged and as playful as her fatigue allowed. Her primary care pediatrician teamed with the pediatric palliative care team at the closest children's hospital and was assisted with many of the decisions about symptom management. In her last days, the patient was on methadone, morphine boluses, lorazepam, citalopram hydrobromide, gabapentin, ondansetron hydrochloride, polyethylene glycol 3350, senna, and as-needed methylphenidate hydrochloride. Her pediatrician made home visits and remained available for evolving symptoms. The pediatrician was in the child's home when the child died.

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CHAPTER 15

Complementary and Integrative Medicine in Pediatric Primary Care

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CASE STUDY

A 14-year-old girl is brought to your office for follow-up on her migraine headaches. She has no other significant medical history but has experienced intermittent migraine headaches over the past few years. The headaches occur approximately weekly in the evenings, do not wake her from sleep, and improve with ibuprofen (400 mg), which was previously prescribed at your office. At this visit, the girl states that she wishes she did not have to take medication for her headaches. Her mother reports that a family friend has suggested acupuncture or herbs for the headaches and asks whether there are other complementary and integrative medicine (CIM) approaches that they could try.

Questions

1. What are CIM therapies?
2. How does a provider explore if any CIM approaches are appropriate for the treatment of chronic or recurrent conditions, such as headaches, in a child or an adolescent?
3. What is the best way to determine whether a family is using CIM?
4. What is the best way to communicate with a family about CIM therapies?
5. What is the best way to monitor the safety of CIM approaches?

Complementary and Integrative Medicine

Complementary and integrative medicine (CIM) refers to a wide variety of therapies that are not typically part of "conventional" medical approaches. Conventional medicine (sometimes called *Western medicine*) is the general approach of medical doctors, doctors of osteopathy, and allied health professionals. The specific therapies thought of as CIM when compared with conventional medicine may change over time as research on CIM practices grows and those that are found to be of benefit are incorporated into evidence-based conventional medicine.

CIM therapies may be used in a number of different ways. When CIM therapies are used by patients in addition to the therapies recommended by conventional medical providers, they are termed *complementary;* this is by far the most common way CIM therapies are used. *Alternative medicine* refers to therapies used instead of conventional care. Increasingly, health professionals are incorporating both conventional approaches and evidence-based nonconventional approaches into their practice, a practice referred to as *integrative medicine.* Complementary and alternative medicine has been used as the umbrella term to describe CIM, but in view of the rare use of these modalities in place of conventional medicine and the increasing use of an integrative approach, *integrative medicine* is replacing *alternative medicine* in many settings, including the National Institutes of Health (NIH) National Center for Complementary and Integrative Health (NCCIH), formerly known as the National Center for Complementary and Alternative Medicine (NCCAM).

Pediatricians are learning about and using integrative therapies in a variety of ways. Many pediatric clinicians review evidence in the medical literature for specific therapies in certain clinical scenarios and integrate approaches into their clinical practice that show potential for benefit and safety. Interested clinicians may also attend continuing education courses and/or trainings in integrative approaches to gain knowledge and skills that can be incorporated into direct patient care. At many institutions, exposure to integrative medicine has expanded during residency training, including didactic and experiential instruction. In addition, a small but growing number of pediatric clinicians have received extensive training in integrative medicine at the fellowship level. Thus, a broad spectrum of approaches to pediatric integrative medicine currently exists.

Epidemiology

The use of CIM has risen steadily over the past several decades and now comprises a significant subset of health-related visits and expenditures. In 2012, 33.2% of American adults surveyed reported having used some form of CIM in the previous 12 months. Out-of-pocket expenditures for CIM totaled $30.2 billion in 2012, up from $27 billion in 1997. These statistics demonstrate the importance of physician awareness of CIM and support the routine inclusion of questions about CIM in the medical history.

A growing body of evidence reveals that the pediatric population is also using CIM. A large-scale survey of caregivers revealed that approximately 1 in 9 children uses CIM (11.6%). Higher prevalence, up to 60%, has been found among certain populations, such as children with cancer, epilepsy, sickle cell disease, or another chronic disease. The most commonly used CIM modalities are dietary supplements, chiropractic or osteopathic manipulation, yoga, and deep breathing exercises. A survey in 2017 revealed that use of yoga by children and use of meditation by children had increased over the previous 5 years from 3.1% to 8.4% and from 0.6% to 5.4%, respectively. Complementary and integrative medicine therapies are most likely to be used for back or neck pain, head or chest cold, anxiety or stress, and other musculoskeletal conditions. Adolescents are more likely to use CIM than younger children. Other factors associated with CIM use by children include parental education beyond high school; higher household income; coverage by private health insurance; use of prescription medications; and number of health conditions, doctor visits, or school days missed for illness in the past year. Non-Hispanic white patients are more likely to use CIM than Hispanic patients or black patients, although the strength of this association diminishes when data are adjusted for confounding factors. When worry about cost prevents the receipt of conventional medical care, children are more likely to use CIM. The strongest predictor of CIM use by children is CIM use by a parent; children whose parents use CIM are 5 times more likely to use CIM. When discussing CIM with families who are using it for their children, pediatricians need to be aware that parents may also be using CIM.

Motivations for Using CIM

Complementary and integrative medicine can be used for health maintenance; for symptomatic relief, as an adjunct to curative conventional medical care; for relief from adverse effects of conventional medical care; or in place of conventional medical care. Families choose to use CIM for many reasons. Word of mouth and belief in the efficacy of the treatment can be strong motivators. Some parents express a desire for more options and feel a sense of empowerment in their parental role as a result of CIM use. Complementary and integrative medicine may also be more congruous with a family's values, philosophies about health, and understanding of the basis of disease. Parents may fear the adverse effects of conventional medications or be dissatisfied with the care their child receives in conventional medical settings. Families may seek the additional personal attention afforded by CIM providers. For some families, CIM offers additional hope when conventional medical care fails. Underlying all these motivations is the desire for the child's health and well-being and the quest for safe and effective treatments of disease. Physicians and families can find common ground in this most basic of motivations, which can inform conversations about CIM and conventional medical care.

CIM Categories

Complementary and integrative medicine therapies can be thought of as falling into 5 categories: whole medical systems, mind-body therapies, biomechanical therapies, bioenergetic therapies, and biochemical therapies (Table 15.1). Besides whole medical systems, these categories are chosen to reflect purported similarities in the underlying mechanism of effect. A particular therapy may be used as part of a whole medical system approach or on its own. For example, acupuncture may be part of an individualized, comprehensive traditional Chinese medicine (TCM) treatment approach, also consisting of herbs and lifestyle recommendations, or a standardized acupuncture treatment may be used without evaluation and treatment by a TCM provider, in which case it can be thought of as a bioenergetic therapy. In addition, a particular therapy may belong to more than 1 category; for example, herbal preparations may have a biochemical and placebo (mind-body) effect.

Whole Medical Systems

Whole medical systems, including conventional medicine, are whole-system approaches to treatment, consisting of an underlying theory of healing, standardized training, and diagnostic and treatment approaches reflective of the underlying theory. For instance, TCM is based on the theory that illness and symptoms result from yin-yang energy imbalances. These energy imbalances are diagnosed through history and physical examination and treated by altering the energy balance using acupuncture (or other mechanical or thermal stimuli), herbs, and lifestyle changes (eg, diet, sleep, physical activity).

Mind-Body Therapies

Mind-body therapies are intended to enhance the mind's ability to benefit health. A number of mind-body therapies are integrated into conventional medical treatment, such as psychotherapy, group therapy, imagery, and biofeedback. Others are still considered CIM, such as meditation and hypnotherapy.

Biomechanical Therapies

Biomechanical therapies aim to improve health through physical manipulation of the body. This may involve working with muscles (as with massage) or spinal alignment (as with chiropractic and osteopathic approaches). Massage therapies range from relatively light muscle work to deep tissue massage and may be incorporated into physical therapy to work with muscles and joints. Spinal manipulation therapies are used commonly in the United States and are most often practiced by chiropractors or doctors of osteopathy.

Table 15.1. Selected Examples of Complementary and Integrative Medicine Therapies by Category			
	Modality	***Description: At a Glance***	***Licensure and Regulation***
Whole Medical Systems	Ayurveda	Originated in India several thousand years ago and is still used by 80% of the population exclusively or in combination with Western medicine. Health and disease are thought to relate to a person's constitution (prakriti), which is composed of a unique combination of the 3 life forces (doshas). Imbalances between the doshas can lead to disease. Treatments are tailored to the individual's unique constitution and are aimed at eliminating impurities, reducing symptoms, increasing resistance to disease, reducing worry, and increasing harmony in the patient's life. Treatments include herbs, vitamins and minerals, massage, yoga, enemas, and specialized diet and lifestyle recommendations.	Ayurvedic medicine is not accredited in the United States, although several states have accredited Ayurvedic schools. In India, Ayurvedic medicine can be studied at the bachelor and doctorate levels.
	Native American healing	Broad term that encompasses the healing traditions of hundreds of indigenous tribes. Has been practiced in North America for >40,000 years. Can combine religion, spirituality, herbal medicine, shamanic healers, purification activities, and symbolic rituals in the treatment of medical and emotional problems. Treatments may be individual or may involve the entire community. Treatment is often a slow process that is spread over days and weeks. There is a strong belief in the therapeutic value of the relationship with the healer.	There is no government oversight of education of or licensure for Native American healers.
	Naturopathy	Developed in Germany and the United States in the late 19th to early 20th centuries. Central belief is that nature has healing power; practitioners view their role as supporting the body's inherent ability to restore health. Naturopathic practitioners strive to use the most natural, least invasive approach to restore and maintain health. Treatment modalities used by naturopaths include nutrition, vitamins and minerals, herbal medications, homeopathy, therapeutic massage and joint manipulation, hydrotherapy, exercise, and lifestyle counseling.	Naturopathic physicians (ND or NMD degree) complete a 4-year graduate-level program at a naturopathic medical school accredited by the Council on Naturopathic Medical Education, which is recognized by the US Department of Education. States vary in their licensing of naturopathic physicians and the scope of naturopathic practice, including the ability to prescribe drugs, perform minor surgery, and assist in childbirth. The American Association of Naturopathic Physicians (www.naturopathic.org) is the national professional society of naturopathic physicians.
	TCM	Originated in China >5,000 years ago; rooted in the Taoist philosophy. TCM practitioners view the human body and mind as an integrated whole in which tissues, organs, and parts function interdependently. Yin-yang theory—the concept of 2 opposing but interdependent forces that shape the world—is a core principle. Health and disease relate to balance between yin and yang in the body. Treatments to restore balance include herbs, massage, acupuncture, diet, and exercises such as tai chi and qigong.	Most states license acupuncture but vary in their inclusion of other TCM treatments in licensure. Acupuncture and TCM schools are accredited by the federally recognized Accreditation Commission for Acupuncture and Oriental Medicine.

(*Continued*)

Table 15.1. Selected Examples of Complementary and Integrative Medicine Therapies by Category (*continued*)

	Modality	*Description: At a Glance*	*Licensure and Regulation*
Mind-Body Therapies	Biofeedback	Technique that trains people to improve their health by controlling certain bodily processes that typically happen involuntarily, including heart rate, blood pressure, muscle tension, and skin temperature. Biofeedback practice involves attaching the patient to electrodes (or other monitoring devices) that monitor the desired process (eg, muscle tension, skin temperature). The therapist leads the patient in exercises designed to assist in controlling the desired variable, while the electrodes provide real-time feedback on the patient's success. Biofeedback is used to treat a variety of conditions, including high blood pressure, headaches, chronic pain, and urinary incontinence.	The Biofeedback Certification International Alliance certifies individuals who have met their educational and training standards, which include didactic training, supervision hours, patient sessions, and case manifestations. Treatment of pelvic floor muscle dysfunction is a subspecialty within biofeedback that requires specialized training. Only licensed health care professionals may apply for certification in this specialty.
	Hypnotherapy	Hypnotherapists use exercises that bring about deep relaxation and an altered state of consciousness, also known as a trance. Through hypnosis, people learn how to master their own states of awareness. By doing so, they can affect their own bodily functions and psychological responses. Hypnotherapy has been studied in treatment of a number of conditions, including state anxiety (eg, before medical procedures or surgeries), headaches, smoking cessation, pain control, hot flashes in breast cancer survivors, and irritable bowel syndrome. It is also used in managing pain during childbirth.	Most hypnotherapists are licensed MDs, registered nurses, social workers, or family counselors who have received additional training in hypnotherapy. Several national bodies provide training certificates. The American Society of Clinical Hypnosis (www.asch.net) is the largest organization of health care professionals using clinical hypnosis and provides hypnotherapy training.
	Meditation and mindfulness	There are many types of meditation, most of which originated from ancient religious and spiritual traditions. Some of these include mindfulness meditation, transcendental meditation, and Zen Buddhist meditation. Through meditation, a person learns to focus attention. Some forms of meditation instruct the practitioner to become mindful of thoughts, feelings, and sensations and to observe them in a nonjudgmental way. Meditation is believed to result in a state of greater calmness, physical relaxation, and psychological balance and can change how a person relates to the flow of emotions and thoughts. Meditation has been studied in a variety of populations and is used for general wellness and various health problems, including anxiety, pain, depression, stress, insomnia, and physical or emotional symptoms that may be associated with chronic illnesses such as AIDS and cancer.	There is a broad diversity of meditation practices, each of which may have its own training programs and certification policies. There is no national or state-based accreditation for meditation practitioner education or licensing. However, meditation programs may be eligible for continuing education credits toward licensing for health care professionals. The University of Massachusetts Medical School Center for Mindfulness in Medicine, Health Care, and Society (www.umassmed.edu/cfm) is a long-standing mindfulness program associated with an academic institution and is a source of training and research on mindfulness and mind-body medicine.
	Yoga	Yoga practice was developed in ancient India, with fully developed practice appearing around 500 BCE. There are numerous branches or paths of yoga. Derived from the Sanskrit word meaning "union," yoga strives to connect the body, breath, and mind with the goal of energizing and balancing the whole person. Yoga practice can be individual or class based and consists of physical postures (asanas), breathing exercises, and meditation. Yoga is used for maintaining health and has also been studied in treatment of a wide variety of conditions, including anxiety, arthritis, asthma, cancer, back pain, diabetes, heart disease, pregnancy (when modified for pregnancy), and chronic headaches.	There is no government oversight of yoga training or practice. Numerous organizations and training programs in the United States and worldwide offer training. The Yoga Alliance (www.yogaalliance.org) is the most widely recognized educational and professional organization for people who teach yoga in the United States. It accredits yoga training programs using a minimum training standard. Teachers who complete Yoga Alliance–accredited training are eligible to become Registered Yoga Teachers.

Table 15.1. Selected Examples of Complementary and Integrative Medicine Therapies by Category (*continued*)			
	Modality	***Description: At a Glance***	***Licensure and Regulation***
Biomechanical Therapies	Alexander technique	Educational method that emphasizes changing faulty postural habits to improve mobility and performance. Treatment has 2 components: table work (hands-on manipulation) and guided activity, in which the practitioner observes the person in action and gives verbal, visual, and physical cues to help the person perform the activity with greater ease. People use the Alexander technique to improve performance in performing arts and sports as well as in treatment of musculoskeletal problems, repetitive stress injuries, and chronic pain.	To be certified by the American Society for the Alexander Technique (www.amsatonline.org), practitioners must complete 1,600 hours of training over 3 years. There is no government oversight of training or licensure.
	Chiropractic care	Developed in the United States at the end of the 19th century. Based on the notion that the relationship between the body's structure—most notably the alignment of the spine—and its coordination by the nervous system affects health. People most often seek chiropractic care for musculoskeletal concerns (back, neck, and shoulder pain), headaches, and extremity problems. Hands-on spinal adjustment and manipulation is a core treatment in chiropractic care, but treatment can also include heat and ice, electrical stimulation, exercise, and counseling about diet, exercise, and lifestyle.	Chiropractic practitioners must meet the licensing and continuing education requirements of the states where they practice. All states require chiropractors to complete a DC degree at an accredited college The American Chiropractic Association (www.acatoday.org) is the largest professional organization representing DCs.
	Feldenkrais Method	A method of somatic education that uses gentle movement and directed attention toward movement patterns to expand movement options and improve functioning. Treatment can be carried out via verbal guidance in a class setting or with hands-on gentle manipulation. People use the Feldenkrais Method to maintain well-being and enhance performance in performing arts and athletics, as well as in the treatment of a variety of conditions, including multiple sclerosis, stroke, cerebral palsy, and repetitive stress injuries.	Feldenkrais Method practitioners must complete 700–800 hours of training over 3–4 years to apply for certification. Certification and training is governed by the Feldenkrais Guild of North America (www.feldenkrais.com). There is no government oversight of training or licensure.
	Massage therapy	Massage therapy has been in use for thousands of years in diverse cultures, including those of China, Japan, India, Egypt, and Europe. The term *massage therapy* encompasses >100 distinct techniques, but the core practice is manipulation of the muscles and soft tissues of the body using the hands and fingers. People use massage for general wellness, as well as to treat a wide range of conditions, including sports injuries, stress, pain, musculoskeletal concerns, anxiety, and depression.	Most states have laws regulating massage therapy and typically require a minimum number of training hours and passage of a national examination. Massage training can be accredited by state boards or an independent agency. The National Certification Board for Therapeutic Massage and Bodywork (www.ncbtmb.org) certifies massage practitioners who pass a national examination. The American Massage Therapy Association (www.amtamassage.org) is the nation's largest professional organization for massage practitioners.
	Osteopathy	Developed in the United States at the end of the 19th century. Core principle is that disease and illness begin with structural problems in the spine and result in abnormalities in the function of the nervous system. DOs not only receive conventional medical training but are also trained in osteopathic manipulation techniques and craniosacral therapy, both of which involve hands-on manipulation of bones and tissues. People seek care from DOs in conventional medicine and specifically for musculoskeletal conditions.	DOs complete a 4-year training program in conventional medicine and osteopathy and also complete medical residencies in their specialty of choice. DOs are recognized for full practice rights in all 50 states once they are licensed. The American Osteopathic Association (http://osteopathic.org) is the primary professional organization and accreditation agency for DOs in the United States.

(*Continued*)

Table 15.1. Selected Examples of Complementary and Integrative Medicine Therapies by Category (*continued*)

	Modality	*Description: At a Glance*	*Licensure and Regulation*
Bioenergetic Therapies	Acupuncture	Acupuncture is a modality of TCM. The earliest recorded use of acupuncture dates from 200 BCE. The core principle of acupuncture is the belief that a particular type of life force or energy (chi) circulates through the energy pathways (meridians) in the body. Chi maintains the dynamic balance of yin and yang. An imbalance of chi can cause symptoms and disease. Acupuncture treatment involves stimulation of specific points along the meridians using pressure (acupressure), thermal energy (moxibustion), or very fine acupuncture needles. Acupuncture has been studied in treatment of a variety of conditions, including chronic pain, postsurgical recovery, chemotherapy-related nausea, musculoskeletal problems, headaches, substance use, asthma, and menstrual problems.	Most states require a license to practice acupuncture, although licensing and education standards vary from state to state. Licensure confers the degree of LAc. In 1997, the NIH recognized acupuncture as a mainstream medicine healing option with a statement documenting the procedure's safety and efficacy for treating a range of health conditions. The American Academy of Medical Acupuncture (www.medicalacupuncture.org) maintains a database of licensed physicians who are also trained to perform acupuncture.
	Homeopathic remedies	Developed by a German physician at the end of the 18th century. Based on 2 core principles: the principle of "similars" ("like cures like") states that a disease can be cured by a substance that produces similar symptoms in a healthy person, and the principle of dilutions ("law of minimum dose") states that the lower the dose of the medication, the greater its effectiveness. Homeopathic remedies are so dilute that few or no molecules of the healing substance remain in the diluent. It is believed that the substance has left its imprint, which stimulates the body to heal itself. Homeopathic remedies are derived from natural substances that come from plants, minerals, or animals.	Homeopathic remedies are prepared according to the guidelines of the *Homoeopathic Pharmacopoeia of the United States,* which was written into federal law in 1938. The US FDA requires that homeopathic remedies meet legal standards for strength, purity, and packaging, but because they contain little or no active ingredients, they are not subject to the same safety and efficacy testing as other over-the-counter medications. If a homeopathic remedy is claimed to cure a serious disease such as cancer, it needs to be sold by prescription.
	Reiki	Developed in Japan in the early 20th century. Based on the idea that a universal energy supports the body's innate healing abilities. Practitioners seek to access this energy, allowing it to flow to the body and facilitate healing. During treatment, the practitioner's hands are placed lightly onto or just above the client's body, palms down, using a series of 12–15 hand positions to promote the flow of energy. Each position is held for 2–5 minutes. People use Reiki for relaxation, stress reduction, symptom relief, and general well-being. It can also be used to help promote peace at the end of life.	No licensing or government accreditation exists for the training or practice of Reiki. Multiple organizations offer training programs and certifications.
	Tai chi	Originated in ancient China as a component of TCM. Rooted in the principles of yin-yang balance and the balanced flow of a vital life force or energy (chi). There are many different styles, but all involve slow, deliberate movements that flow into each other. Meditation, deep breathing, and maintenance of good posture during continuous movement are foci of the practice. People use tai chi to improve overall fitness, balance, coordination, and agility. It is also used to treat chronic pain, gout, heart disease, high blood pressure, arthritis, osteoporosis, diabetes, headaches, and sleep disorders.	No licensing or government accreditation exists for the training or practice of tai chi. A variety of organizations offer training programs and certification in tai chi.

Table 15.1. Selected Examples of Complementary and Integrative Medicine Therapies by Category (*continued*)			
	Modality	***Description: At a Glance***	***Licensure and Regulation***
	Therapeutic touch	Developed in the 1970s in the United States. Based on the belief that problems in the patient's energy field that cause illness and pain can be identified and rebalanced by a healer. The technique consists of using the hands to release harmful energy and direct healthy energy for healing purposes. During a session, the hands are held 5–15 cm (2–6 in) away from the body and there is no direct physical contact between practitioner and patient.	No licensing or government accreditation exists for the training or practice of therapeutic touch. Multiple organizations offer training programs, including some hospitals. Many therapeutic touch practitioners are nurses or other licensed health care professionals.
Biochemical Therapies	Nutritional approaches	Nutritional approaches are an integral part of many whole medical systems, including Ayurveda, TCM, and naturopathy (see the Whole Medical Systems section in this table). Numerous specialized diets have been promoted as offering benefits of health maintenance, weight loss, or treatment of disease. Examples of diets that have demonstrated evidence of benefit in adult randomized controlled trials include the DASH (Dietary Approaches to Stop Hypertension) diet, low carbohydrate diets (such as the Atkins diet), the Mediterranean diet, and a plant-based diet. Few specialized diets have been studied in treatment of the pediatric population.	Certification of registered dieticians is controlled by the Academy of Nutrition and Dietetics (www.eatright.org). Forty-seven states currently regulate licensure and certification of dieticians. Dieticians in Integrative and Functional Medicine is a specialty practice group within the Academy of Nutrition and Dietetics composed of practitioners who self-identify as using an integrative approach to nutrition (https://integrativerd.org).
	Dietary supplements	Dietary supplements contain ≥1 dietary ingredient, including vitamins, minerals, herbs, or amino acids, or their constituents. Herbal medications are considered a subset of dietary supplements in the United States. Some dietary supplements have been proven to prevent or treat disease (eg, folic acid in the prevention of neural tube defects, calcium and vitamin D in the prevention of osteoporosis), while other claims about dietary supplements are unproven. The most commonly used dietary supplements are fish oil, *Echinacea,* flaxseed, ginseng, multivitamins, vitamins E and C, calcium, and vitamin B complex.	In the United States, dietary supplements can be sold without being tested to prove they are safe and effective. They must be made according to good manufacturing practices. In the United States, no organization regulates the manufacture or certifies the labeling of dietary supplements.
	Herbal medicine	Herbal medicine refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Plants have been used for medicinal purposes since long before recorded history in a wide range of human cultures. According to the World Health Organization, 80% of the world's population relies on herbal medications for some part of their primary care. Nearly one-third of Americans use herbs. The most commonly used herbal supplements in the United States include *Echinacea,* St. John's wort (known botanically as *Hypericum perforatum)*, gingko, garlic, saw palmetto, ginseng, goldenseal, chamomile, feverfew, ginger, valerian, evening primrose, and milk thistle. Herbal remedies are used in conventional medicine as well as a variety of CIM practices, including naturopathy, TCM, Ayurveda, and Native American healing. Many people also use herbal remedies on their own, without the advice of a health care professional.	In the United States, herbal supplements are classified as dietary supplements and can thus be sold without being tested to prove they are safe and effective. They must be made according to good manufacturing practices. In the United States, no organization regulates the manufacture or certifies the labeling of herbal preparations.

Abbreviations: BCE, before the Common Era; CIM, complementary and integrative medicine; DC, doctor of chiropractic; DO, doctor of osteopathy; FDA, Food and Drug Administration; LAc, licensed acupuncturist; MD, medical doctor; NCCIH, National Center for Complementary and Integrative Health; ND, naturopathy doctor; NIH, National Institutes of Health; NMD, naturopathy medical doctor; TCM, traditional Chinese medicine.

Information in this table is adapted from the health topics pages at the NCCIH website (https://nccih.nih.gov) and the American Cancer Society "Complementary and Alternative Medicine" page (www.cancer.org/Treatment/TreatmentsandSideEffects/ComplementaryandAlternativeMedicine/index).

Bioenergetic Therapies

Bioenergetic therapies are directed at improving health through altering the body's energy as it runs through, on, or around the body. Because conventional training does not include the concept of energy in this way, bioenergetic therapies tend to draw skepticism from conventional medical providers. With increasing scientific evidence of its beneficial effects, acupuncture is purported to affect the body's vital energy (chi) as it courses through energy channels called *meridians.* In 1997, an NIH consensus panel declared the evidence sufficient for integration of acupuncture into a number of conventional treatments, including treatment of chemotherapy-associated nausea and emesis, anesthesia-associated nausea and emesis, and pain syndromes. Homeopathic remedies are theoretically bioenergetic therapies, as the "ingredients" are successively diluted beyond the point of significant molecular presence; therefore, it is the resulting change in the energy of the diluents (sometimes called the "memory of the molecule") that is responsible for the therapeutic effect. In addition, a number of therapies aim to affect energy at or near the surface of the body, including therapeutic touch and Reiki, both of which involve a trained practitioner identifying the energy imbalance and directing the patient's own energy to improve the patient's energy balance and promote healing.

Biochemical Therapies

Biochemical therapies are intended to improve health through their biochemical effects and include nutritional approaches, herbal remedies, and dietary supplements. Nutrition is an important part of many CIM approaches, such as Ayurveda, TCM, and naturopathy, and is also an accepted part of the conventional medicine approach to disease prevention and treatment. As the body of research on integrative nutritional approaches has grown, some interventions that originated as integrative approaches, such as the Mediterranean diet, have become part of evidence-based conventional medicine. Herbal remedies and dietary supplements are conceptually related to the biochemical mechanism of effect of conventional medications but have a few important differences. First, herbal remedies are by nature complex mixtures of chemicals, so their effects are likely caused by multiple biochemical reactions. Second, there is currently no federal regulation or oversight of the production of herbs or supplements in the United States, as there is with pharmaceuticals, so quality control is extremely variable. Third, safety concerns are addressed not before they are available commercially to consumers, as with pharmaceuticals, but only after products are on the market and adverse events are reported to the US Food and Drug Administration. Because of the lack of oversight of production and premarket safety, it is important for practitioners to research not only the evidence of an herb's effect and potential adverse effects but also the particular formulation's production and quality control.

Approaching CIM Use From a Conventional Medicine Perspective

As with any treatment option, the safety (risks) and efficacy (benefits) of a CIM modality must form the basis for therapeutic decision-making about its use. Table 15.2 can be a helpful guide in directing physician responses to a particular CIM therapy.

Table 15.2. Guide to Complementary and Integrative Medicine Treatment Recommendations

		Is the Therapy Effective?	
		Yes	**No**
Is the Therapy Safe?	**Yes**	Recommend	Tolerate
	No	Monitor closely or discourage	Discourage

If there is insufficient evidence to assess safety or efficacy

- Establish a plan with the family for monitoring response to treatment.
- Discourage if adverse reactions develop.
- Tolerate if no adverse reactions develop.

Assessing Efficacy

Data on the efficacy of CIM treatments are increasingly available as CIM becomes a greater focus of research effort and funding in the United States and worldwide. When searching the medical literature for CIM evidence, international and foreign-language articles can be useful, as certain CIM modalities may have been studied in greater depth or over a longer period in other countries. As with any research data, it is important to consider study design, outcome measures, sources of bias, methods of data analysis, and applicability of results for a given indication, patient, or patient population. With herbal remedies and supplements, it is also important to acknowledge that formulations differ, so efficacy as reported in a clinical trial may be altered if a different formulation is used.

Assessing Safety

The huge diversity of CIM makes it difficult to discuss safety in general terms. Each CIM modality has its own unique risk profile. However, awareness of broad categories of risk can help physicians prevent bad outcomes.

- *Delay of conventional care:* In studies of CIM risks for the pediatric population, the risk associated with the highest morbidity and mortality rates is delay of conventional care. This delay can come about for a number of reasons, including a family's perception that care from a CIM provider obviates the need for conventional care, a family's inability to afford conventional care, or a family's belief that conventional care will be harmful. It may be helpful to contract with families that they will seek conventional care before or in conjunction with CIM care for a new symptom or acute illness to rule out disease processes that require conventional treatment.
- *Drug-drug interactions:* Certain supplements and herbal remedies may interfere with or alter the effects of conventional medications. Particular attention has been given to substances that are inhibitors or inducers of hepatic drug metabolism by the cytochrome P-450 enzymes, with St. John's wort (used for depression; known botanically as *Hypericum perforatum*) and grapefruit juice being the most well-known examples. See the Resources for Physicians section for online

resources for checking drug-drug interactions with herbal remedies and supplements.
- *Adverse reactions:* Allergic reactions, adverse effects, and idiosyncratic reactions are possible with CIM therapies as well as conventional therapies. Close follow-up is helpful in monitoring response to therapy.

Regulation and Licensure

Licensure and accreditation for CIM providers varies from state to state. Chiropractic care, massage therapy, acupuncture, naturopathy, and homeopathy have licensing bodies in some states. In states where licensing exists for a CIM modality, it is incumbent on the physician to ensure that any referrals are made to licensed practitioners. None of these licenses authorizes the practitioner to practice medicine. Other CIM modalities may have a national organization that supervises training and certifies practitioners. Although these are not subject to government oversight, there still may be value in preferentially seeking out providers who are approved by their national organization, as these providers have had to meet a standard established by their colleagues.

Regulation of herbal remedies and supplements is the subject of ongoing scrutiny and debate. Currently, the US Food and Drug Administration does not regulate production or marketing of these products, so it is often difficult to verify their composition, safety, or efficacy unless they have been independently studied. The burden of researching products and manufacturers falls to the consumer.

Communication About CIM Use

Most caregivers of children who use CIM do not disclose this use to their pediatrician despite that most report a desire to discuss it. The high rate of nondisclosure is alarming, as it places patients at risk for drug-drug interactions with conventional medications, robs physicians of the opportunity to monitor for adverse reactions, and interferes with the development of trust in the patient-physician relationship. Reasons cited by patients and caregivers for nondisclosure include
- Negative experiences with past disclosures to physicians.
- Fear of disapproval or judgment on the part of physicians.
- Belief that physicians do not need to know.
- Lack of time with physicians.
- Physicians do not ask.

Many of these barriers can be addressed by the physician.

Physicians may be reticent to discuss CIM, as evidenced by the fact that CIM discussions are patient initiated in most cases. Physicians may worry about legal liability if there is a bad outcome. They may fear conflict with families over use of CIM. They may be afraid to reveal their lack of knowledge about CIM and may worry that this lack of knowledge will threaten a family's trust in their abilities. They may feel pressured by time constraints and overwhelmed by the need to acquire new knowledge. There is often a disconnect between the meaning that patients and families attribute to CIM use (more options and a greater sense of empowerment) and the meaning that physicians may attribute to it (irrationality given lack of evidence and the threat of interference with conventional medical care). This disconnect can influence patients and physicians to avoid the subject of CIM.

Communication Tips

Effective communication about CIM use is a wonderful opportunity to improve rapport and better understand a patient and family (Box 15.1). Communication can be a powerful tool for ensuring safety and reducing harm, as well as for broadening physician knowledge and building trust with families. Even if they do not initiate or recommend a CIM treatment, pediatricians can play an important role by monitoring a child's response to the treatment over time and engaging the family in a discussion about risks and benefits if adverse reactions arise. Discussion about CIM may also bring about a greater understanding of families' explanatory models of illness as well as their expectations of health care professionals and their beliefs about conventional medications. Deeper insight into a family's health beliefs and values can facilitate a more successful patient-physician partnership and better patient care.

Box 15.1. Complementary and Integrative Medicine Communication Tips

- Make questions about complementary and integrative medicine (CIM) use a routine part of the medical encounter.
- Pose questions about CIM use in an open and nonjudgmental way. For example, "For me to take the best possible care of your child, it is helpful to know about all the ways your family manages health and illness. Are there any treatments, medications, herbs, or supplements that your child uses but we have not talked about yet? Does your child see any other providers for health-related care or treatments?"
- Explore details of CIM use. Ask families not only what CIM modalities they are using but also why they chose each treatment, how it works, whether they have noticed a difference, and if there have been any downsides to the treatment.
- Validate the family's desire for health and well-being for their child.
- Do not be afraid to acknowledge the limits of your knowledge. If asked to provide a recommendation about an unfamiliar CIM modality, offer to do further research, and revisit the question at a follow-up visit.
- Seek out information about CIM, including literature on safety or efficacy.
- Involve families in the thinking process of comparing risks with benefits of a CIM intervention or modality. Provide evidence-based advice when possible. If there is little or no evidence to support or discourage use of a CIM modality, share this information with families.
- Make a plan with families to monitor their child's response to treatment, including measurable outcomes (eg, symptom relief, increased quality of life) and any adverse effects.
- Encourage families to share information about CIM use continually, even if they choose to continue a treatment about which you have raised concerns.
- Document CIM-related discussions in the medical record.

CASE RESOLUTION

Explaining that CIM is not your area of expertise, you ask the family to return in 1 week to discuss this further. After consulting the NCCIH website and conducting a brief review of the medical literature, you find that there are data on efficacy and safety of CIM therapies for migraine headache prevention, including acupuncture and self-hypnosis. At the follow-up visit, you discuss these options with the family. The girl is interested in both modalities but decides to try acupuncture first. You offer her support for this choice and ask that she keep close track of her headaches and return in 1 month to let you know how she is doing with the acupuncture treatments and her headaches.

Resources for Physicians

CAM on PubMed
https://nccih.nih.gov/research/camonpubmed
The NCCIH provides a link to a PubMed search box that is limited to the CIM subset of PubMed.

Cochrane Complementary Medicine
https://cam.cochrane.org/evidence
Link to more than 700 Cochrane reviews on CIM interventions. The Cochrane Collaboration is an independent, international network of leaders in the health care field who are committed to helping health care professionals make evidence-based decisions. Subgroups devoted to specific topic areas produce systematic reviews of available evidence of health-related interventions. The CIM-related subgroup is coordinated through the University of Maryland School of Medicine Center for Integrative Medicine.

ConsumerLab.com
www.consumerlab.com
This for-profit organization carries out independent testing of dietary supplements and herbal remedies by request of manufacturers and for the benefit of the public. In either case, samples for testing are obtained not directly from the manufacturer but from the consumer marketplace. The ConsumerLab.com seal that appears on vitamin bottles can be purchased by manufacturers once their product has been tested by ConsumerLab.com.

Medscape Drug Interaction Checker
https://reference.medscape.com/drug-interactionchecker
Free website that offers users the opportunity to look up drug-drug interactions and includes herbal supplements as well as conventional prescription and over-the-counter medications.

National Center for Complementary and Integrative Health at the National Institutes of Health
https://nccih.nih.gov
The NCCIH is the federal government's lead agency for scientific research on CIM. The website provides information about CIM modalities for providers and patients, results of clinical trials supported by NCCIH, lists of ongoing trials, and information about training and funding opportunities in the field of CIM.

Natural Medicines (Product Information)
https://naturalmedicines.therapeuticresearch.com
Subscription-based site that includes evidence-based information on CIM modalities as well as online tools to check for drug-drug interactions.

NSF International
www.nsf.org/services/by-industry/nutritional-products
An independent organization that tests and certifies a wide range of products and systems, including dietary supplements. Before certifying a product, NSF International performs toxicology tests to ensure that the contents match what is on the label and that the product does not contain unhealthy levels of contaminants such as heavy metals, pesticides, or herbicides.

USP
www.usp.org/dietary-supplements-herbal-medicines
A nonprofit organization that develops and publishes standards for strength, quality, and purity of drugs, dietary supplements, and food ingredients. Dietary supplements must meet these standards to display a USP Verified Mark on their labels.

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CHAPTER 16

Principles of Pediatric Surgery

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CASE STUDY

A 4-month-old boy is evaluated by his pediatrician for swelling in the groin and is diagnosed with a right inguinal hernia. His parents are told that their child will be referred to a pediatric surgeon. The parents are concerned about surgery in such a young infant and ask their pediatrician multiple questions. Is he big enough to have surgery? Will he be able to eat before the surgery? Will he be in pain? Will he need to have blood drawn? Will he need to be hospitalized? Will he be put to sleep for the procedure?

Questions

1. What are the typical questions parents ask if their child is undergoing surgery?
2. What is the role of the primary care physician in advising patients and parents about surgical procedures?
3. What is the role of the surgeon in advising patients and parents about the surgery?
4. What are general guidelines for feeding infants and children prior to surgery?
5. What are the risks of general anesthesia in infants and children?
6. How long is the hospitalization after surgery?
7. How do physicians prepare children who are about to undergo surgery?
8. What laboratory studies are needed prior to surgery?

No matter the age of the patient, the prospect of surgery is generally anxiety-provoking for the patient and the patient's parents. As with any stressful patient encounter, communication is the key to educating, calming, and reassuring patients and their parents. This is particularly true in case in which patients are being referred, even initially, for surgical consultation. Pediatricians can provide significant support by giving the parents basic information about surgical care. It is also important for primary care physicians and surgeons to communicate with each other to provide the highest level of care.

Preoperative Care

Initial Consultation

When a surgical problem is suspected, the first task of the primary care physician is to initiate a referral to a pediatric or general surgeon. The purpose of the initial surgical visit is to confirm the diagnosis and discuss surgical and, if applicable, nonsurgical, treatment options. Surgical procedures are rarely performed during this consultation, and this fact should be stressed by the primary care physician prior to the surgical consult. Many children and parents mistakenly think that surgery will occur at the time of the first encounter and are therefore unduly anxious. Some parents even schedule time off from work unnecessarily with the expectation of having to provide postoperative care for their child, and they become disappointed and even angry when the surgery is not performed. Sometimes the diagnosis of the primary care pediatrician is incorrect, in which case the surgeon can reassure parents about the correct diagnosis and advise them that surgery is not necessary.

The parents and children are given a significant amount of information during the surgical consultation. A referring diagnosis is either confirmed or not, and a decision is made about whether the patient requires an operation. If surgery is indicated, it is described in detail to the parents and, if age-appropriate, to the patient as well. A thorough review of the risks and benefits of as well as any alternatives to the procedure is undertaken. An estimate of how long the procedure will take is given. A general discussion on the expected recovery is conducted, such as whether the procedure will be performed as outpatient or inpatient, where hospitalization occurs, how long the child will miss school, and whether any activity restrictions exist.

Parents and patients should be encouraged to compile a list of questions before their first clinic visit to make sure that questions are not left unanswered. Parents and patients should also write down the answers to refer to them at a later time. Typical questions include the length of time of the procedure itself, the use of anesthesia, and the length of recovery time. If parents agree to proceed with surgery, the surgeon starts the process and paperwork. Often, this is the only visit required before the date of the operation. However, some hospitals require patients to be seen by the surgeon within 30 days of the procedure; thus, a return visit may be required if the date of surgery is beyond that time frame. Additionally, some hospitals and surgery centers require patients to undergo a preoperative evaluation by the anesthesia team prior to surgery.

Preparation of Anesthesia for Infants and Children

Anesthesia is extremely safe in infants and children, and the risk of a poor outcome from general anesthesia is less than 1% at most institutions. Specialized pediatric anesthesiologists provide anesthetic care for infants and young children. If a pediatric anesthesiologist is not available, anesthetic care for infants and children is often limited to a set of experienced general anesthesiologists. Parents and patients often experience anxiety about undergoing anesthesia. Videos have been created and are available at many institutions to help explain the anesthesia process. These videos have been shown to increase medical knowledge and decrease anxiety about undergoing anesthesia.

Many types of anesthesia exist, including moderate sedation (ie, conscious sedation), regional anesthesia, and general anesthesia. Typically, the type of anesthesia is determined by the surgeon and anesthesiologist; however, the anesthesiologist makes the final decision. Although the least amount of anesthesia is desired, all patients must be treated as though they may require general anesthesia in case moderate sedation or regional anesthesia is inadequate to provide the required anesthesia for the individual operation.

To minimize the risk of aspiration when undergoing general anesthesia, the stomach must be empty of food and liquids. Although each hospital has its own specific policies, Box 16.1 lists frequently recommended guidelines for the interval between meals and surgery. In general, most infants and children must miss 1 meal before surgery. Often, it is possible to replace this meal with clear liquids.

All medications should be continued unless otherwise directed by the surgeon or anesthesia staff, and they can be taken with a small sip of water on the morning of surgery. It is also recommended that the parents or guardians bring a list of the child's medications on the day of the operation so that the surgical staff can review the list preoperatively.

Box 16.1. Guidelines for the Interval Between Eating/Drinking and Surgery in Infants and Children

<6 Months of Age

- 4 hours for human milk/formula
- 2 hours for clear liquids[a]

6–36 Months of Age

- 8 hours for solids
- 6 hours for human milk/formula
- 2 hours for clear liquids[a]

>36 Months of Age

- 8 hours for solids/milk
- 2 hours for clear liquids[a]

[a] Formula, milk, orange juice, and colas are *NOT* considered clear liquids. Clear liquids include any liquid that can be seen through (eg, water, sugar water, apple juice, Jell-O, broth).

Laboratory Studies

Laboratory studies, such as complete blood cell count, electrolyte panel, and/or blood typing, should be performed if indicated by the patient's underlying comorbidities or current disease process. Blood products may be needed during or after surgery if there is blood loss. If blood loss is anticipated, parents or other family members will be given the option to directly donate blood prior to the procedure. Direct donation of blood can take days to weeks depending on the specific blood bank, however, and it may not be an option for urgent or emergent operations. Additionally, the cost of directly donating blood is often the responsibility of the patient. If primary care physicians need laboratory tests performed for other reasons, often the necessary blood work can be obtained while the patient is under anesthesia.

Imaging Studies

The parents or guardians should bring with them to the surgical consultation copies of any imaging studies obtained by the primary care physician. Hard copies or electronic files of the imaging itself as well as the final report by the radiologist are strongly recommended. If imaging studies are needed for further workup or preoperative planning, these studies can be ordered later by the surgeon. If studies are to be ordered preoperatively by the primary care physician, that physician should contact the surgeon to confirm which specific studies to order. This communication will avoid obtaining unnecessary studies or the need to repeat any studies that were not done appropriately.

Patients Requiring Urgent/Emergent Surgery

Patients with acute conditions often present first to their pediatrician or primary care physician. Common conditions include abdominal pain consistent with appendicitis, an abscess requiring drainage, an incarcerated hernia, or vomiting caused by pyloric stenosis. Such patients should be directed to the emergency department (ED) for further workup and management, and the pediatric surgeon should be notified. Any time a patient is sent to the ED for a possible surgical issue, it is essential to remind the parents to not give the patient anything to eat or drink (ie, nil per os [NPO]). If parents feed patients en route to the ED, treatment will be delayed because of anesthesia-related concerns. The NPO guidelines in Box 16.1 are enforced even in urgent conditions; only in life-threatening emergencies may the guidelines be disregarded. In most acute situations, patients are often dehydrated as a result of vomiting, poor oral intake, or third-spacing of fluid. Thus, it is essential that patients be adequately resuscitated preoperatively. A standard intravenous (IV) fluid resuscitation of 20 mL/kg of lactated Ringer injection or normal saline should be administered, followed by continuous administration of maintenance (or slightly higher rate of) fluids. Appropriate antibiotics also should be administered as indicated. Patients with acute appendicitis should be started on single-, double-, or triple-agent broad-spectrum antibiotics depending on their symptoms and the preferences of the surgical team. Patients with abscesses should be administered

antibiotics with excellent gram-positive coverage, with special attention to methicillin-resistant *Staphylococcus aureus*, given its high prevalence. Pain medication is given as needed. It is rare that a true surgical condition is masked by the appropriate dose of pain medication; thus, pain medication can be given even if the surgeon has not yet evaluated the patient. Finally, basic laboratory studies, such as a complete blood cell count and electrolyte panel, should be obtained.

Perioperative Care

The final operating room schedule for elective cases is often made the day before surgery. Thus, the specific time of an elective procedure is not known until 1 day prior to surgery. Often the surgeon can give parents an estimated start time. Families are contacted the day before surgery to confirm the time of the procedure as well as when and where to arrive. Patients are typically asked to arrive 1.5 to 2 hours before the scheduled start time to allow sufficient time to ensure patient safety by completing all necessary steps before the actual operation.

In general, patients are put under anesthesia when they arrive in the operating room. For infants and young children, an IV line is placed after the patient is asleep. To minimize anxiety, preanesthetic sedation is administered orally before proceeding to the operating room. Once in the operating room, patients are often administered an inhalational anesthetic, followed by placement of the IV line, then intubation. Some institutions allow parents to accompany their child to the operating room and see the child put to sleep with the inhalational anesthetic.

After the operation is complete, patients are brought to the recovery room. Parents typically are allowed in the recovery room until the time of discharge. Criteria for discharge from the recovery room are listed in Box 16.2. For children who have undergone outpatient surgery, careful written instructions are provided to parents along with dates and times of follow-up appointments as well as telephone numbers for use should problems arise. Children who have undergone inpatient procedures are discharged from the recovery room to the pediatric inpatient service, along with appropriate orders for nursing personnel. Child life specialists are available at many institutions to help acclimate patients to the hospital and perioperative setting. These specialists provide information, comfort, and reassurance, and they offer general positive reinforcement to patients.

Box 16.2. Criteria for Discharge After Outpatient Surgery

- Patient is stable and exhibits age-appropriate vital signs
- Age-appropriate ambulation
- Ability to tolerate oral fluids
- No bleeding
- No respiratory distress
- No pain that cannot be controlled by oral medication
- Age-appropriate alertness

Controversy persists about the postoperative management of former preterm infants after undergoing general anesthesia because they are at increased risk for postoperative apnea. Reasonable recommendations for typical outpatient operations include overnight admission with apnea monitoring for former preterm infants who were born at 52 weeks' postconception age or younger. However, each institution has its own specific policy, and the exact age for required admission varies. The decision for admission is also based on the patient's current health and comorbidities and should be made by the surgeon, anesthesia team, primary care physician, and the patient's parents. Table 16.1 lists the most common elective and urgent/emergent operations and anticipated postoperative hospitalization stays.

Table 16.1. Common Elective and Urgent/Emergency Operations and Anticipated Postoperative Hospitalization

Type of Procedure	*Procedure*	*Length of Hospitalization*
Elective	Inguinal hernia repair	None[a]
	Umbilical hernia repair	None[a]
	Cyst excision	None[a]
	Central venous catheter insertion/removal	None[a]
	Orchiopexy	None[a]
	Laparoscopic cholecystectomy	None[a]
	Lymph node biopsy	None[a]
	Ostomy takedown	3–4 days
	Lung resection	3–4 days
	Imperforate anus repair	3–4 days
	Pectus excavatum repair (ie, Nuss procedure)	4–5 days
Urgent/Emergency	Laparoscopic or open appendectomy for nonperforated appendicitis	1–2 days
	Laparoscopic or open appendectomy for perforated appendicitis	5–7 days
	Pyloromyotomy	1 day
	Intussusception reduction	1 day
	Bowel resection	5–7 days
	Bowel obstruction	5–7 days
	Tumor resection (ie, Wilms tumor or neuroblastoma)	7 days
	Choledochal cyst or portoenterostomy	5–7 days
	Pull-through for Hirschsprung disease	5–7 days

[a] Outpatient procedure.

Postoperative Care

Parents often call their child's primary care physician with questions postoperatively; thus, it is important that the physician be knowledgeable about routine postoperative care. Most children recover from anesthesia and surgery faster than adults. Unless otherwise specified, such as after an appendectomy for perforated appendicitis, a normal diet can be resumed as soon as the patient has an appetite. If patients cannot tolerate a normal diet, a bland diet and plenty of fluids are recommended. Furthermore, unless otherwise specified patients should resume taking all their preoperative medications the evening of or morning after surgery.

Almost all surgical wounds are closed with absorbable sutures and covered with thin adhesive strips. Additional dressings can be removed 1 to 2 days postoperatively or as needed. By 48 hours postoperatively, wounds do not need to be covered unless they are open or there is drainage. Unless otherwise specified, most wounds can be exposed to water (ie, shower, quick bath) 48 hours after surgery. With the exception of thin adhesive strips, dressings should be removed prior to bathing.

The surgeon provides parents and the child details about activity limitations and returning to school. Often, heavy physical activity, such as physical education in school or organized sports, should be avoided until the surgeon sees the patient after discharge. Although heavy physical activity is to be avoided after surgery, patients should be encouraged to walk as well as to cough and breathe deeply many times a day to avoid atelectasis. Patients can return to school when they feel ready and have only minimal pain.

The main reasons to contact the surgeon postoperatively are a temperature above 38.6°C (101.5°F), worsening or persistent pain, persistent emesis, and any wound drainage or redness. Additional instructions specific to the operation are also provided to the parents.

CASE RESOLUTION

In this case, the pediatrician reassured the parents that many patients have been referred to this surgeon. The parents were assisted by the pediatrician in crafting their questions for the surgeon. The surgeon subsequently confirmed the diagnosis of an inguinal hernia and recommended surgery. All details were provided, and the parents' questions were answered. The patient was scheduled for outpatient surgery, and everything went smoothly. Postoperatively, there were no concerns, and the patient saw the surgeon and pediatrician in the course of standard follow-up care.

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CHAPTER 17

Image Gently Approach to Pediatric Imaging

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CASE STUDY 1

A 15-year-old boy comes to your office reporting back pain after exertion for the past week. He reports no significant recent trauma. He plays varsity basketball but has not had any falls during recent games. He is otherwise healthy, with no significant medical history.

The pain does not prevent him from playing sports or attending school. He has no history of prior episodes of back pain. He reports that the pain is relieved by nonsteroidal anti-inflammatory drugs. On physical examination, he has left-sided paraspinal focal tenderness in the L3-L4 region. He has limited range of motion twisting to that side.

CASE STUDY 2

A 10-year-old girl is brought to your office with runny nose, congestion, cough, and headache. You saw this patient 6 weeks ago as well as 4 months ago, when she had similar symptoms. Her mother reports full compliance with the antibiotic regimen you prescribed but states that her daughter's symptoms have never fully resolved. On physical examination, the child is afebrile with purulent nasal discharge. Tenderness to palpation is elicited over the cheeks and forehead.

Questions

1. How does imaging contribute to the diagnosis of a patient's condition?
2. How does the physician determine which imaging studies are appropriate for an individual patient?
3. What is the ALARA principle?
4. What information is available for counseling patients about the risks of diagnostic radiation?
5. Where can appropriate imaging recommendations for pediatric patients be found?
6. Does patient history influence the choice of imaging studies?
   a. Would imaging be appropriate for the patient in Case Study 1 had he recently experienced significant trauma?
   b. Would imaging be appropriate for the patient in Case Study 2? What if her symptoms had been new and begun only the week before this latest office visit?

Overuse of medical imaging is a growing problem in the United States, with financial and medical repercussions. The primary care physician must often decide what, if any, imaging is appropriate for a particular patient. In many situations, clinical assessment and physical examination are adequate for diagnosis. In some instances, however, imaging provides vital information that cannot be adequately obtained from other sources. Patients and their families may also insist on diagnostic imaging based on the belief that the more technologically advanced the evaluation, the better the care.

Approximately 370 million studies using diagnostic radiation are performed annually in the United States (Figure 17.1). The most dramatic increase has been in the use of computed tomography (CT). In 1982, 1 million CT scans were performed in the United States. In 2006, 67 million CT scans were performed, with an estimated 4 to 7 million of these performed in children. In response, many concerned health professionals and radiologists gathered to create the national *Image Gently* Campaign, with a focus on minimizing the use of diagnostic radiation when possible and using appropriate pediatric imaging for children in the United States. Because of the widespread attention and highly concerted efforts of the organizations involved in this effort, several recent studies have observed a slight downward trend in CT use for pediatric patients in the United States. Because of the substantial variation among different imaging practices, however, the opportunity exists for continual improvement.

Basic Concepts

Diagnostic radiology examinations that use ionizing radiation include plain radiography, fluoroscopy, CT, and nuclear medicine. Ionizing radiation may cause damage to DNA molecules. Children are more radiosensitive than adults secondary to children's growth of rapidly proliferating cells and longer life span. Certain organs are more radiosensitive than others, and children in particular are at an increased risk for breast cancer, thyroid cancer, and leukemia.

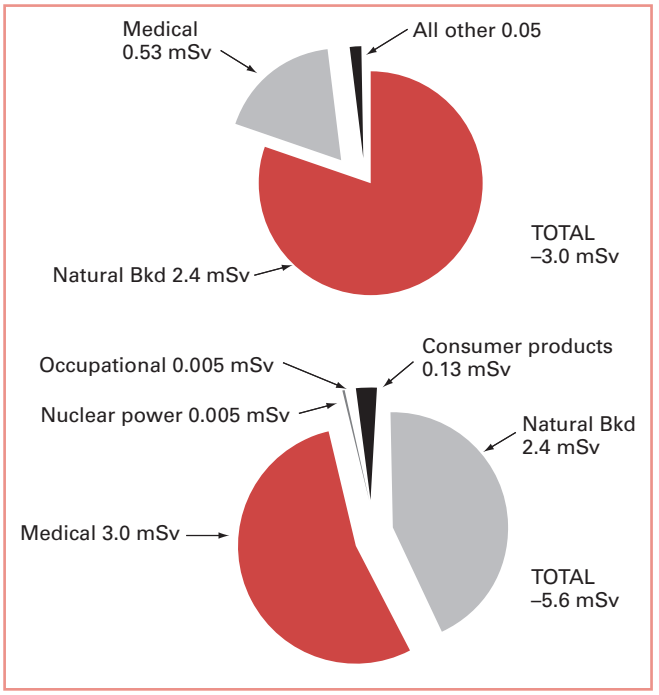

Figure 17.1. Charts showing the United States annual per capita effective radiation dose from various sources. Upper: Chart for 1980. Lower: Chart for 2006.

Abbreviation: Bkd, background.

Reprinted with permission from Mettler FA Jr, Bhargavan M, Faulkner K, et al. Radiologic and nuclear medicine studies in the United States and worldwide: frequency, radiation dose, and comparison with other radiation sources—1950-2007. *Radiology.* 2009;253(2): 520–531, with permission.

Table 17.1. Comparison of Radiation Dose by Imaging Procedure Type for Pediatric Patients

Diagnostic Procedure	*Typical Effective Dose (mSv)*[a]	*Number of Chest X-rays for Equivalent Effective Dose*	*Number of Days of Background Radiation for Equivalent Effective Dose*
Chest x-ray (PA)	0.02	1	72
Skull x-ray	0.07	3.5	255
Lumbar spine	1.3	65	159
Upper GI	3	150	366
Barium enema	7	350	852
Head CT	≤2	≤100	243
Chest CT	≤3	≤150	366
Abdomen CT	≤5	≤250	609

[a] Natural background radiation is 3 mSv per year.

Abbreviations: CT, computed tomography; GI, gastrointestinal; PA, posteroanterior.

Derived from the Image Gently Alliance and the Society for Pediatric Radiology.

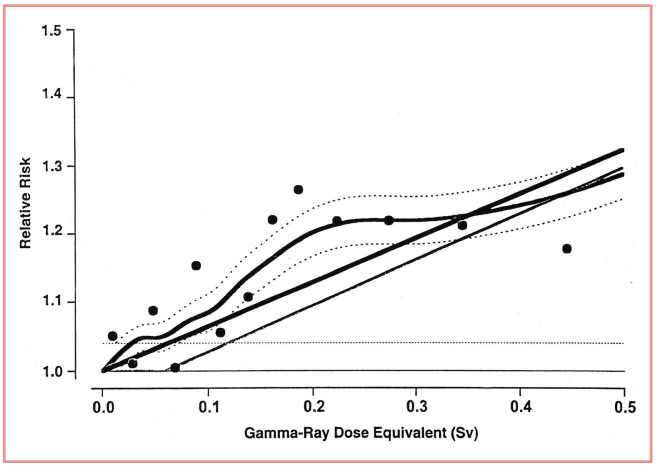

Figure 17.2. Graphic representation of the relative risk of contracting cancer in atomic bomb survivors. The dashed curves represent 61 standard error for the smoothed curve. The straight line is the linear risk estimate computed from the range 0–2 Sv. Because of an apparent distinction between distal and proximal zero-dose cancer rates, the unity baseline corresponds to zero-dose survivors within 3 km of the bombs. The horizontal dotted line represents the alternative baseline if the distal survivors were not omitted.

Reprinted with permission from Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiat Res.* 2000;154(2):178–186.

One of the most common ways to measure radiation dose is by the effective dose, measured in sieverts, which takes into account all the exposed tissues and the relative radiosensitivity of each organ. The effective dose also provides a way to compare radiation dose across different imaging modalities. For example, for children 1 CT scan of the chest imparts an effective dose equivalent to up to 150 chest x-rays (Table 17.1).

The ALARA Principle

In recent years, increasing attention has been paid to and research done on patient radiation exposure from diagnostic imaging. Much of this concern stems from data derived from survivors of the atomic bombs used in World War II. The radiation dose to each survivor was calculated based on each individual's distance from ground zero, and more than 50,000 of these patients were followed for more than 50 years. The data showed an increased cancer risk for many of the survivors. Based on this observation, a mathematical model was created which states that the risk of cancer proceeds in a linear fashion without threshold (Figure 17.2). According to this model, even a small amount of radiation increases the risk of cancer. Current estimates vary concerning diagnostic radiation and the risk of cancer. Based on research by multiple radiation biologists, the American College of Radiology (ACR) estimates that for adults, 1 fatal cancer is induced for every 1,000 CT scans performed. The risk is higher in children, with 1 fatal cancer occurring for every 500 to 1,000 CT scans performed. This figure is superimposed on the national cancer incidence of 42%.

This research spurred the founding of the *Image Gently* Campaign, which stresses a multifaceted approach that is intended to minimize radiation exposure to children. The campaign has brought together 60 medical and professional organizations representing more than 700,000 imaging specialists from the fields of pediatrics, radiology, physics, and radiology

technology. The as low as is reasonably achievable principle (*ALARA principle*) is based on the notion that any amount of radiation exposure, no matter how small, can increase the chance of negative biologic effects. The aim of the ALARA principle is to balance the goals of minimizing the amount of radiation while obtaining sufficient imaging quality, resulting in accurate diagnostic information.

The Role of the Radiologist

The pediatrician can often determine whether any imaging study is needed based on the history and physical examination. In some conditions (eg, acute trauma), imaging is important to assess the nature and extent of the injury. In other conditions, such as infectious processes (eg, cough, symptoms of sinusitis), medical management is warranted initially before any imaging is performed.

Communication and coordination between medical specialists and radiologists is often helpful. When in doubt, a call to the local radiologist, regardless whether that person is a dedicated pediatric radiologist, can guide the specialist in determining which test is reasonable for a specific patient. Radiologists have many means by which to tailor examinations to minimize radiation. The first step often involves asking whether nonionizing diagnostic examinations, such as ultrasonography or magnetic resonance (MR) imaging, can be performed to answer the same diagnostic question. In particular, ultrasonography often can be used as a screening examination to evaluate conditions that can be clarified with other studies that involve radiation if needed. For certain indications, MR imaging is a great alternative to CT; however, in some cases, the need for sedation and other risks of MR imaging may outweigh the risks of CT. Radiologists are also required to monitor equipment and study protocols to ensure radiation dosage does not exceed the recommended range. All commercial CT scanners used in the United States include multiple methods to adjust the radiation dose. A low-dose technique should be used whenever appropriate. Newer-generation CT scanners use a significantly decreased dose while maintaining imaging quality. Breast and gonadal shielding can offer additional protection to children.

Resources for Physicians and Parents

The ACR has established appropriateness criteria for imaging of specific medical conditions and presentations; these criteria were coauthored by clinicians and radiologists. The criteria are available free online and can be downloaded and incorporated into computerized ordering and electronic health record systems (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria).

The Image Gently website (www.imagegently.org) offers educational materials for parents to help them understand the risks and benefits of diagnostic imaging and the associated radiation. The website also has printable child imaging history cards for parental use to track all diagnostic radiation examinations performed on their child (Figure 17.3).

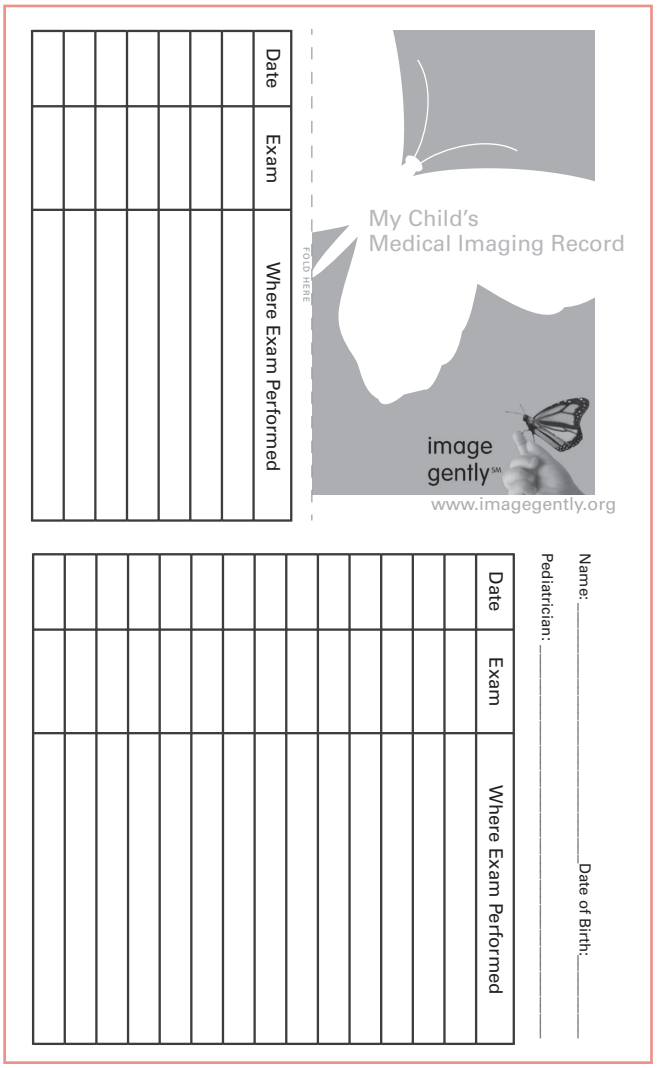

Figure 17.3. Child imaging history card on which parents can record their child's exposure to imaging studies.
Borrowed with permission from the *Image Gently*® Alliance.

CASE STUDY 1

Case Study 1: The Importance of the Patient History

Back pain is a common symptom in active adolescent patients. Many studies have evaluated the use of imaging in patients with atraumatic back pain. In the absence of significant trauma, most studies have found that there is little value in imaging otherwise healthy adolescents who present with musculoskeletal pain. If this patient had experienced significant trauma or demonstrated focal neurologic findings suspicious for significant injury to the spinal cord or a disk, MR imaging would be the most appropriate examination. Radiographs of the spine are not helpful in assessing disk disease or central nervous system injury. Radiographs are helpful in adult patients to evaluate the extent of multilevel disk disease. For this patient, the physician should obtain a comprehensive history and perform a complete physical examination to help define the differential diagnosis and assist in the determination of the appropriate imaging study. See Resources for Physicians at the end of the chapter for a link to the ACR Appropriateness Criteria for back pain in a child.

Case Resolution

The physician should recommend rest, nonsteroidal anti-inflammatory drugs, and stretching exercises for 4 to 6 weeks. If the pain persists after that time, magnetic resonance imaging of the lumbar spine without contrast would be a reasonable next step in the workup of this patient.

CASE STUDY 2

Case Study 2: Symptom Duration and Response to Treatment

Imaging should be obtained in cases of chronic sinusitis that do not respond to treatment and persist for months without resolution. Computed tomography of the sinuses is useful in the evaluation of the soft tissues, extent of disease, and any potential intracranial complications. Computed tomography also provides important anatomic detail should surgery be required. Radiographs have limited utility in evaluation of sinusitis because of the lack of soft tissue, anatomic detail, and low sensitivity. This is particularly true in very young children whose sinuses are not yet well aerated. Imaging is not appropriate in the setting of acute sinusitis in an otherwise well child. See Resources for Physicians at the end of the chapter for a link to the ACR Appropriateness Criteria for child sinusitis.

Case Resolution

The physician should order a computed tomography scan of the sinuses, because the patient has signs and symptoms of chronic sinusitis despite treatment. Had the patient been presenting for the first time with signs and symptoms of sinusitis, medical treatment would be indicated and imaging would be considered were the patient not to respond to that medical management.

Resources for Physicians

ACR Resources

Appropriateness Criteria
www.acr.org/Quality-Safety/Appropriateness-Criteria

Sinusitis
https://acsearch.acr.org/docs/69442/Narrative/

Back Pain
https://acsearch.acr.org/docs/3099011/Narrative/

Radiation Dose Assessment
www.acr.org/-/media/ACR/Files/Appropriateness-Criteria/RadiationDoseAssessmentIntro.pdf

Image Gently website

www.imagegently.org

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CHAPTER 18

Simulation in Pediatric Health Care

Tom Kallay, MD

CASE STUDY

An 8-year-old boy presents to your office for a follow-up appointment after an asthma exacerbation. He reports feeling better while at home this morning, but on the car ride to your office his chest started "hurting," and he began to experience shortness of breath. During his intake he appears to be in a moderate amount of distress, with evidence of tachypnea and tachycardia. His pulse oximeter reports a value of 90%. Your staff administers nebulized bronchodilator therapy and oxygen, and a call is made for paramedic transport to the nearby hospital. Within the next few minutes the staff becomes concerned that he may need emergent airway support, but you are not sure if the equipment is functioning properly since the last time it was used. The paramedics arrive and safely transport the child to a facility that provides a higher level of care. Although emergency interventions were not required during this situation, you and your staff feel that you could have been better prepared. You decide to take measures to optimize the function of your staff and office environment for the rare emergency.

Questions

1. What is simulation?
2. How does simulation apply to health care?
3. What modalities of simulation are available for medical training?
4. How does one create and deliver simulation training?
5. Why should a primary care physician use simulation?

Simulation is a powerful tool for learning. In the most general sense, simulation is a learning technique in which people or technology are used to mimic real-life encounters. These encounters are practiced in simulated conditions, and typically the learner receives performance feedback as if the learner were in the real situation.

Simulation has a long legacy of use for education and evaluation in many high-risk industries. Examples include flight simulators for pilots and astronauts, war games for military personnel, and technical operations for nuclear power personnel. Simulation provides learners of all levels an opportunity to practice and develop knowledge and skills without the threat of causing harm to individuals. Currently, high-risk industries use robust simulation programs that are embedded into the culture of training and skill maintenance. Because health care is a high-risk industry, it seems intuitive that simulation would have a place in medical training, with the purpose of improving patient safety and outcomes.

Simulation in Medicine

History

Simulation in medicine began in 1960 with Resusci Anne, a mannequin designed for mouth-to-mouth resuscitation training. This was a new resuscitation technique conceived by Peter Safar, MD, and James Elam, MD, in 1957, which influenced Norwegian toymaker Asmund Laerdal to create the mannequin for practicing the principles of resuscitation. The airway could be obstructed, necessitating neck hyperextension followed by thrusting the chin forward to insufflate the lungs. An internal spring placed in the chest of the mannequin permitted the practice of cardiac compressions, and subsequently, cardiopulmonary resuscitation (CPR) training was born.

Computer-controlled mannequins were developed in 1967 at the University of Southern California. Medical educator Stephen Abrahamson, PhD, along with anesthesiologist J. Samuel Denson, MD, collaborated with a group of engineers from the Sierra Engineering and Aerojet General Corporation to create Sim One. This prototype device was a computerized, adult-size mannequin that featured breathing, heart sounds, functional pupils, and an anatomically correct airway. It was used for airway management training for anesthesia residents from the late 1960s through the 1970s, with a noted benefit of training without placing patients at risk. Ultimately, however, Sim One did not gain acceptance and the program was terminated. For the next 3 decades, simulation in medical education remained relatively dormant.

The Growth of Simulation in Medicine

...[N]o industry in which human lives depend on the skilled performance of responsible operators has waited for unequivocal proof of the benefits of simulation before embracing it.
—David M. Gaba, MD

The Institute of Medicine (IOM) report *To Err Is Human: Building a Safer Health System*, published in the year 2000, drew attention to the perils of the health care system, highlighting the human and financial costs of medical errors. The period following the IOM report witnessed a resurgence of simulation in medicine as a response to the reinvigorated emphasis on patient safety. Government and medical institutions began to embrace simulation as a means of improving health practitioner and team performance to improve outcomes. In 2001, the Agency for Healthcare Research and Quality (AHRQ) published an analysis of patient safety practices and dedicated a chapter to the potential benefits of simulation.

With the publication of increasing evidence that simulation could be applied to patient safety, it began to find its way into the language of accreditation and certification. The Accreditation Council for Graduate Medical Education has embraced simulation as an effective training method and now mandates that simulation resources be available for programs such as anesthesia and surgery, and more programs are following suit. In 2008, Accreditation Council for Graduate Medical Education program requirements mandated having available simulation resources for 3 out of 159 residency requirements; as of today, that number has grown 10-fold, to 30.

A body of pediatrics literature demonstrating the benefits of simulation has been published. This knowledge has been used to improve skills ranging from complex resuscitations to lumbar puncture (LP) and has demonstrated applicability to inpatient and outpatient settings.

For example, the literature on pediatric outpatient emergencies shows that offices are frequently ill-equipped to manage an emergency. In 2000, the American Academy of Pediatrics Committee on Pediatric Emergency Medicine published *Childhood Emergencies in the Office, Hospital, and Community: Organizing Systems of Care*. This resource highlights how preparation of the staff, office environment, and community are crucial for delivering high-quality emergency care and advises that simulated mock scenarios or codes are an essential part of an office emergency preparedness plan. Currently, many resources provide the necessary tools for providing simulation education in the field of pediatrics.

Simulation is increasingly used in the health care field. In 2004, the Society for Simulation in Healthcare was established by professionals who use simulation for education, testing, and research in health care. Members now include physicians, nurses, allied health and paramedical professionals, researchers, and educators from around the globe, and the society hosts an annual meeting. Since 2006, the AHRQ has been funding simulation research as part of its safety mission. This research has expanded our knowledge on how to effectively use simulation in a variety of clinical settings. Additionally, the AHRQ in collaboration with Society for Simulation in Healthcare created the *Healthcare Simulation Dictionary* to provide uniform terminology and definitions for users of health care simulation. In response to demand, the medical simulation equipment industry has blossomed, and currently products that can simulate virtually any situation encountered in medicine are available. With the development of not only the technology but the technique of simulation, it has become apparent that for health care, as in other high-stakes industries, simulation has found its place.

This chapter provides a broad overview of simulation in health care—the associated terminology, available resources for health care education, and techniques for providing this mode of training.

Terminology

The term *simulator* refers to the equipment, such as a simulated arm for venipuncture, a computerized mannequin that replicates human physiology, or a virtual reality computer with programming designed to practice laparoscopic surgery. *Simulation* is an educational technique described by the IOM in 2010:

> *The act of imitating a situation or a process through something analogous. Examples include using an actor to play a patient, a computerized mannequin to imitate the behavior of a patient, a computer program to imitate a case scenario, and an animation to mimic the spread of an infectious disease in a population.*

Simulation-based medical training is a systematically designed program that provides information, demonstration, and practice-based learning activities that are supported by the concept of deliberate practice.

A *simulation center* is an area designed to provide some or all of the aforementioned modes of simulation. It can range in size from a 60 m^2 room to a 3,000 m^2 building replicating a hospital with fully equipped patient rooms, clinics, and operating rooms. Such centers provide opportunities to practice all facets of medicine, depending on the learning goals. Spaces can be fashioned to appear like an emergency department or clinic office and may be wired with cameras and microphones so that learner actions and statements can be recorded and reviewed for evaluation and feedback. Some centers may use a control room adjacent to the simulation area, separated by 1-way mirrors, that allows the facilitator to observe and control the scenario without being in the room with the learner. If high-fidelity mannequins are used, they are controlled from this room via computer, and facilitators communicate with role players in the scenario by 2-way radio. There may be conference areas for viewing live simulations and debriefing, as well as storage areas for equipment. Multidisciplinary centers provide the best opportunity for cross-training among health professionals and building camaraderie.

In situ simulation comprises simulation activities embedded in an actual clinical environment. The advantage of in situ simulation is that medical scenarios can be practiced in the working environment, thereby providing the closest approximation of reality. Such simulation is excellent for team training, because all members of the medical staff can participate. Another advantage of in situ simulation is that it provides the ability to test the working environment for conditions that can predispose a person to make an error.

For example, a prospective randomized controlled trial was performed to evaluate the effect of a simulation-based intervention designed for emergencies in the pediatric office. Thirty-nine

practices were involved, with 20 in the intervention group and 19 serving as controls. The intervention involved 2 mock codes delivered by the investigators in the office (in situ), where staff responded using their own equipment and local emergency medical services. After the mock code, the investigators debriefed the staff, reviewed existing emergency equipment, and assisted with developing a resource manual designed for emergencies. A post-intervention survey was distributed 3 to 6 months later that included items on the following areas: purchase of new emergency equipment or medications; receipt or updating of basic life support, pediatric advanced life support, and advanced life support certification by staff members; and development of written protocols for emergencies. The control group received no intervention and completed the same survey.

Intervention practices were more likely than control practices to develop written office protocols (60% vs 21%; $P = 0.02$), and staff in intervention practices were more likely to be current on life support certifications by the time of the post-intervention survey (118 vs 54; $P = 0.02$). No significant differences existed between the 2 groups in terms of the purchase of new equipment or medications. Satisfaction with the simulation exercise was evaluated as well. At the time of the post-intervention survey, 90% of staff felt the exercise was useful for their practice, and 95% felt that the program should be continued.

Although in situ simulation is an effective tool, it does have shortcomings. In a busy hospital or clinic environment, staff may feel overburdened by having to perform extra tasks during work hours that may be perceived as unnecessary. It is the responsibility of the person organizing a simulation practice session to ensure that patient care is not compromised during the activity; it is also important to build a culture of patient safety in which staff feel a responsibility to provide excellent individual and team function in a well-prepared environment.

Medical Simulation Resources

Resources available for simulation in health care can be categorized into 1 of 5 areas: mannequin based, screen based, virtual reality, task trainers, and standardized patients (SPs) (Box 18.1). How these tools are used depends on the educational needs.

Mannequins are lifelike representations of human beings and range in size from a preterm neonate to a full-size adult. The spectrum of functionality spans from a simple form, such as Resusci Anne, to a high-fidelity mannequin. A *high-fidelity mannequin* is computer driven and has features that represent human physiology, such as breathing, heart sounds, and blood pressure. These mannequins are technology dependent and often expensive and require expertise in maintenance and operation. Mannequins are typically used for mock codes, which can be applied to almost any health care setting, such as an office, inpatient ward, or operating room.

Box 18.1. Resources for Medical Simulation Training

- Mannequin: simple or computer driven
- Screen-based simulation programs
- Virtual reality programs
- Task trainers
- Standardized patients

Screen-based simulated programs are more affordable and logistically easier than a mock code. Unlike a mock code, which often requires the coordination of more than 1 person, screen-based simulated programs can be performed by an individual at any location with a computer. Software programs are available that contain libraries of clinical scenarios in which patient history, examination findings, image studies, and laboratory tests can be represented graphically. Users can select diagnostic and therapeutic options as they work through the case and generate a record of performance. Immediate feedback is provided by preprogrammed software or an instructor at a later time.

Task trainers are three-dimensional representations of body parts that allow the user to improve technique or develop psychomotor skill in many areas, such as intravenous line insertion, LP, or bag-valve mask. Task trainers exist for nearly every procedure and discipline, with options ranging from preterm neonates to adults. Some trainers provide visual, auditory, or printed feedback to the learner based on the quality of the performance. For example, when practicing bag-valve mask on a baby head, an airway connected to inflatable lungs allows learners to visualize the effectiveness of their technique. Task trainers are especially useful for practitioners to gain familiarity with the equipment being used, whether they are first learning to use the equipment or refreshing their skills after a period of nonuse.

Virtual reality and haptic systems use the most sophisticated computer programming for procedural practice. *Virtual reality* refers to the re-creation of environments or objects as a complex, computer-generated image. *Haptic systems* provide the capability of tactile learning, and these programs can provide detailed feedback on procedural skill based on the kinetic actions of the user. Typically, virtual reality and haptic systems are used with a task trainer; most of the products available are for vascular access, surgical procedures, bronchoscopy, or endoscopy. Evidence shows that virtual reality is superior to traditional training; it is likely that simulation-based medical education will further incorporate virtual reality in the future. Currently, virtual reality programs are relatively cost-prohibitive and limited in scope; however, this may change as programming and options continue to develop.

Standardized patients have been used in graduate medical education for years. An SP is an actor playing a role and provides trainees an opportunity to practice communication, physical examination skills, or history taking. Although SPs typically play the role of a patient, they can also play the role of a family member or a fellow health practitioner.

Hybrid simulation, which combines 2 modes of simulation for a more realistic experience, is an excellent opportunity to provide a multifaceted learning experience. For example, when creating a scenario for a child with diabetic ketoacidosis (DKA), a mannequin

and an SP can incorporate scripts written for DKA as well as for a mother who must be told that her child has a new diagnosis of diabetes mellitus. Learners have the opportunity to both apply their knowledge in assessing and treating DKA and use their skills in having difficult conversations. Afterward, feedback is provided to the learners about their medical knowledge, decision-making skills, and communication skills. The term *confederate* is sometimes applied to role players who work together with the instructor in scenarios.

Technique

The Culture of Simulation

This section describes the elements that are needed when designing and delivering education using simulation. But before these steps are illustrated, it is important to discuss the culture of simulation learning and how it fits with the current culture of medicine.

Traditional medical education emphasizes the importance of error-free practice, with intense pressure to achieve perfection during diagnosis and treatment. Furthermore, when mistakes are made, the psychological toll for the practitioner cannot be underestimated. It is often said that there are 2 victims in the case of a medical error: the patient and the health professional. Reports of provider depression, substance abuse, and suicide highlight the need for engendering a productive rather than destructive response to medical errors, which is 1 of the central aims of simulation. The technique of practicing technical skills or decision making skills in an environment absent of the "shame and blame" response can assist in developing healthy reactions to mistakes, in which the factors leading to the error are objectively reviewed and analyzed and improvements instituted. When a mistake is made, the goal is to change the thinking from what the repercussions will be to how health professionals can better themselves to improve care for their patients. As the practice of medicine is an art, so is the practice of becoming a better health professional.

The learning environment for simulation education activities must connote a safe learning environment in which mistakes can be made without reproach. In fact, simulation is an area in which it is desirable for health professionals to make mistakes so that the practice of improvement can occur. It is the responsibility of the facilitators to explicitly state this to help create an atmosphere conducive to constructive discussion.

Simulation activities also provide an opportunity for health professionals to train together and build effective communication skills and team camaraderie. The training of health professionals—nurses, physicians, medical or physician assistants—generally occurs in parallel, which can have the unintended consequence of poor communication between team members. This potentially can create an environment that may not always be conducive to fair and open discussion of mistakes, which is necessary if optimal learning and improvement are to occur. When delivered with creativity and enthusiasm in a nonthreatening environment, simulation can provide a venue for building effective relationships between practitioners while imparting educational benefits.

Steps for Delivering Simulation Learning

Developing simulation activities requires multiple steps and careful planning to achieve learning goals (Box 18.2). Health professionals are often busy and have little spare time, so in addition to making simulations accessible, the educational product must be sound and worth the time spent. Learning events that are not well planned or delivered can have an adverse effect on an individual's perception of simulation education, which can have a negative effect on that person's learning. The first step in delivering simulation learning is the creation of a mock code or scenario, followed by deliberate practice, a concept of instruction that is applicable to scenario or procedural training.

Mock Scenario Development

The first step in creating a scenario is to identify what needs to be improved; this may be related to medical knowledge, technical skill, communication, team function, or a combination of these. Adverse as well as routine events in the office or hospital setting often provide opportunities for learning and improvement and can set the educational framework.

The case study provided in the beginning of the chapter, for example, highlights a situation in which a mock code could be helpful in improving performance. Practicing a mock scenario of anaphylaxis can address multiple needs: teamwork, communication, locating and operating equipment, performing proper advanced life support techniques, and disposition. After a scenario is developed, it can be practiced by the office staff until performance standards are met.

When writing a mock code or scenario, the first task is to create succinct learning objectives. Writing clear objectives is an underappreciated skill and is a crucial part of any educational program. Good objectives are important because they focus teaching and enable the evaluation of the effectiveness of the activity. A helpful way to start thinking about objectives is to begin with the phrase, "By the end of this session, the learner will be able to..." followed by the

Box 18.2. Steps for Providing Simulation-based Medical Education

1. Determine learning needs.
2. Create learning objectives.
3. Create learning lesson.
   a. Script, if performing mock scenario.
   b. Simulated patient history and physical examination, laboratory data, images, and case progression.
   c. Consequences of anticipated interventions and disposition.
   d. Identification of required equipment and space.
   e. Identification of role-players.
4. Session delivery.
   a. Create a safe learning environment.
   b. Deliberate practice.
5. Feedback/debriefing.
   a. Advocacy inquiry.
   b. Plan for improvement.

learning objective. Objectives should be specific and measurable and use words that are open to few interpretations. For example, the objective, "By the end of the session, the learner will understand the complications of bag-mask ventilation.", is open to many interpretations, whereas the statement, "By the end of the session, the learner will be able to list the complications of bag-mask ventilation.", is open to fewer interpretations.

The learning objective in the first example is vague; it may be answered in multiple ways. Additionally, the instructor does not have a clear standard for how to measure what has been learned. The second objective not only focuses the teacher and learner but provides a concrete way to measure knowledge by requesting a finite list. Depending on educational needs, typically 2 to 4 objectives are sufficient for a session. The use of too many objectives can be overwhelming and can have a dilutional effect on the knowledge being imparted. Box 18.3 provides examples of words that are open to fewer or more interpretations.

After the learning objectives are established, a script is written that describes the flow of events and consequences of anticipated interventions. A list of required equipment or props, role-players needed with instructions on how to act, a history and physical examination of the simulated patient, and laboratory tests or images are also included. It is helpful to write the scenario such that an individual other than the writer can use it for future sessions. Eventually, if multiple scenarios are written, a catalog of cases with various clinical scenarios can be developed that can serve as a sustainable learning resource. Many templates are available that can be helpful in writing a scenario, with varying degrees of complexity. The important thing is for instructors to use the method that fits their time and needs.

After preparation is complete, the session can be delivered. How well the instructor introduces the simulation learning experience can set the tone for all that follows. Before any simulation begins, the facilitator helps participants clarify what is expected of them and helps them understand the benefits and limitations of the simulated clinical setting. Learners must understand whether and how the case, event, or procedure will later be debriefed (ie, discussed and analyzed) and whether the simulation will be video recorded. The instructor must explicitly state that the focus is on learning, not on catching people in a mistake. This helps create an environment in which participants feel safe in sharing thoughts and feelings about the upcoming simulation and debriefing without fear of being shamed or humiliated.

Participants often worry that simulations are designed to expose their weaknesses or humiliate them. To counter these thoughts, facilitators should convey the understanding that learners have good intentions and are trying to do their best but will likely make mistakes. Learners should be reassured that mistakes are desirable in the simulation environment because they provide focus on areas in need of improvement, which in turn can result in improved patient care.

After the scenario is complete, the next step is to debrief the case. This is the time to review the stated objectives; however, the overall goal of debriefing is to allow trainees to explain, analyze, and synthesize information and emotional states to improve performance in similar situations in the future. This can be challenging, because voicing critical thoughts can result in hurt feelings or defensiveness on the part of the learner. It is the responsibility of the instructor to lead a discussion that encourages objective reflection of practice without being confrontational.

One general framework of inquiry commonly used is: "What went well? What did not go well? What could we do to improve next time?" This gives participants the opportunity to voice their opinions and concerns. The techniques helpful for good debriefings are designed to increase the chances that the learner will process what the instructor is saying rather than become defensive. Advocacy-inquiry is 1 technique that can be used to help guide debriefing sessions.

Advocacy-inquiry is founded in the theory of reflective practice, which is a means of analyzing one's own work practices and examining the foundation of their existence. When incorrect actions are performed, the goal of debriefing is to elicit the framework of the participants' thought processes, which have been formed by their knowledge and experience. There may have been a previous situation in which an instructor provided incorrect information or in which miscommunication occurred that may have had a significant formative effect on the learner's understanding and subsequent behavior.

An advocacy is an observation, whereas an inquiry is a question. When the 2 are paired together, instructors state in the advocacy their hypothesis and test the hypothesis with an inquiry in a nonthreatening manner. For example, during a mock code drill for a patient with asystole, the instructor notices that cardiac compressions were not started immediately. During the debriefing, the instructor might say to the learner, "So, I noticed that you were working on providing oxygen to the patient after you noticed the lack of a heart rate" (ie, advocacy). "I was thinking there was possibly an additional maneuver to be done. I'm curious—how were you seeing the situation at that time?" (ie, inquiry). Rather than making

Box 18.3. Words or Phrases Open to More or Fewer Interpretations

Open to More Interpretation

- Know
- Understand
- Be able
- Know how
- Appreciate
- Grasp the significance of
- Learn

Open to Fewer Interpretations

- List
- Recite
- Demonstrate
- Perform
- Rank (ie, rank as important)
- Describe

a judgmental comment, such as, "Do you realize that it took you 2 minutes before you started chest compressions?", the instructor is using advocacy-inquiry to elicit the learner's framework of thinking that guided the learner's actions. The participant might state, "I was once admonished during my training for not doing things in the right sequence." Having elicited this description of a prior training experience, the instructor has an opportunity to refine the thought process of the learner.

Just as the delivery of simulated scenarios requires practice, so does the facilitation of a productive debriefing process. In 2007, Rudolph et al published a good article on learning the technique of debriefing.

Although simulated clinical scenarios and mock codes are complex processes, the task of teaching procedures is generally more straightforward. An excellent framework for teaching procedures in a simulated environment involves using the concept of deliberate practice.

Deliberate Practice

Education research has demonstrated that acquisition of expertise in medicine or other fields (eg, professional sports, musical performance, chess) is based on a set of principles governed by the concept of deliberate practice, which is among the cornerstones of simulation-based medical education. To summarize, *deliberate practice* dictates that the learner will engage in repetitive performance of cognitive or psychomotor skills with direct assessment, which provides the learner with feedback tailored to improve performance. The elements of deliberate practice are listed in Box 18.4.

Coupled with simulation, deliberate practice has been shown to improve performance in many medical and surgical specialties. Studies ranging from general pediatrics to vascular surgery have demonstrated improvements in skills, knowledge, and team function when simulation with deliberate practice is used.

A randomized, controlled trial evaluated the effectiveness of deliberate practice simulation-based training compared with audiovisual training only for improving infant LP skills among pediatric residents. After a baseline assessment of LP skill and knowledge, all participants viewed an educational audiovisual presentation. The intervention group went on to participate in a simulation-based deliberate practice session on an infant LP simulator. The primary outcome was self-reported clinical success on the first infant LP after training. Fifty-one residents reported on 32 LP encounters; 94% of the intervention group reported success, compared with 47% in the control group, a marked difference. When the residents were evaluated on an observed clinical examination at 6 months, however, no difference was found between the groups. These findings suggest that although simulation training with deliberate practice is effective, skills decline over time and continual practice and retraining are necessary.

In adult medicine, a randomized trial with wait-list controls evaluated the acquisition of advanced cardiovascular life support skills among internal medicine residents using a mannequin simulator. Residents who received the simulation-based medical education with deliberate practice scored 38% higher on a reliable skills evaluation than residents in the wait-list control group. After crossover and a deliberate practice session with the control group, the scores surpassed the performance outcomes of the first intervention group. The authors concluded that deliberate practice, in addition to time and experience, is helpful in achieving competence.

The concept of close observation by experts with provision of constant real-time feedback can be applied to almost any procedure. However, deliberate practice is only 1 tool in achieving procedural excellence; continual practice is a key component to maintaining a high level of performance.

Box 18.4. Features of Deliberate Practice

1. Highly motivated learners with good concentration
2. Engagement with a well-defined learning objective or task
3. Appropriate level of difficulty
4. Focused, repetitive practice
5. Rigorous, precise measurements
6. Informative feedback from educational sources (eg, simulators, instructors)
7. Monitoring, correction of errors, and more deliberate practice
8. Evaluation to reach a mastery standard
9. Advancement to another task or unit

Adapted with permission from McGaghie WC, Siddall VJ, Mazmanian PE, Myers J; American College of Chest Physicians Health and Science Policy Committee. Lessons for continuing medical education from simulation research in undergraduate and graduate medical education: effectiveness of continuing medical education. American College of Chest Physicians Evidence-Based Educational Guidelines. *Chest.* 2009;135(suppl 3):62S–68S.

Benefits of Simulation

Despite all the points demonstrating that simulation is a valid teaching tool for medical training, concerns exist about its role. The time taken away from real patient experience, significant effort and time required to create and deliver simulation training, cost of equipment, and potential for humiliation are all points that cause trepidation. Furthermore, the question remains whether it is effective.

Simulation is an evolving science, and a growing body of evidence indicates that it can be effective in improving medical knowledge and skills, team function and communication, and patient safety and outcomes and that its use can result in hospital cost savings in terms of return on investment. Health care payers and liability insurers have noticed simulation as the potential effects on patient safety are now being realized. For the development of the health professional, simulation does not and should not replace the benefits of real patient experience; however, it can serve as an important component in the professional's education. After an individual grasps the technique, simulation education can be provided without the use of elaborate and expensive simulators but instead (with some creativity) with the use of lower-cost materials. The future of simulation in medicine depends on the dedication and ingenuity of the health care simulation community to see that improved patient safety and educational outcomes can be realized using this method. Potential benefits and applications of simulation are outlined in Box 18.5.

Box 18.5. Benefits and Applications of Simulation

- Avoidance of risks to patients and learners
- Tailoring of procedural training or scenarios to educational need and attributes of the learner
- Practicing of skills and scenarios as many times as necessary
- Enhancing transfer of skills from the classroom to the clinical arena
- Determination of educational needs
- Training for optimal team or organizational function
- Practicing communication skills
- Providing opportunity to practice rare critical events
- Assisting in the testing of new equipment or facilities
- Refresher training for staff at all levels
- Serving as formative or summative assessment tool at all levels

Conclusion

Health care simulation is a technique to augment real experiences with guided, interactive encounters that approximate reality. The past 25 years have witnessed tremendous growth in the health care training industry, with applications in medical education and patient safety practices. Simulation provides a training method that does not place patients at risk and that can be tailored to meet the needs of learners at any level. When delivering simulation education, it is important to highlight to participants the goal of improvement and acceptance of errors to connote a safe learning environment. Additional work is required to continue to advance this technique to assist in improving the health care system for patients.

CASE RESOLUTION

You and your staff review what occurred in the case of the child who experienced a severe asthma exacerbation and identify the educational and environmental needs of your practice. You determine that your educational objectives are related to accessing the emergency equipment, having well-defined staff roles when advanced life support measures are required, and providing effective bag-valve mask ventilation. You obtain an inexpensive mannequin to serve as a model for the child and write the script of the case. You discuss with your office staff what your plans are and that the goal is to improve office function in emergent situations. You schedule an appropriate time and deliver the mock scenario with the entire office staff. It is discovered that some of the equipment is not operational, and some staff members voice a lack of confidence in their bag-valve mask skills, which they have not had to use for some time. A practice session is held in which staff members can practice the skill of bag-valve mask ventilation on the mannequin and receive constructive feedback on technique. Afterward, you lead a discussion with the group, review the points that require improvement, and develop a plan to rectify the equipment issues, knowledge gaps, and skills gaps. The mock code intervention was universally well received by the staff, and confidence in the ability to manage emergent situations in the office setting was improved.

Resources for Physicians

Healthcare Simulation Dictionary
www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/research/simulation-dictionary/index.html

Society for Simulation in Healthcare
www.ssih.org

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CHAPTER 19

Pediatric Hospital Medicine

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CASE STUDY

A 15-month-old girl presents to a community hospital emergency department with fever, cough, and rhinorrhea. On initial evaluation, she is found to be in moderate respiratory distress, with decreased air movement and scattered bilateral wheezes and crackles on lung examination. Her oxygen saturation is 87% on room air and rises to 96% with the application of 1 L/min of supplemental oxygen via nasal cannula. The physician diagnoses the patient with bronchiolitis and treats with nebulized albuterol and an oral dose of prednisone. The hospital has no inpatient pediatric service, so the emergency physician calls the local children's hospital to arrange a transfer. The emergency physician signs the patient out to a hospitalist, who accepts her onto the inpatient pediatric service and arranges for ground basic life support transport.

Questions

1. What is the role of hospitalists in inpatient pediatric care?
2. How can hospitalists implement principles of family-centered care and evidence-based medicine into the clinical care of hospitalized children?
3. How can hospitalists promote quality improvement and patient safety in the hospital setting?
4. What communication strategies can hospitalists use to ensure safe transitions of care within the hospital and back to the outpatient medical home after discharge?

Introduction

Every primary care physician (PCP) must periodically make the decision to hospitalize a patient who can no longer be cared for effectively in the outpatient setting. In 2015, 2.1% of all children and teenagers younger than 18 years, or more than 1.5 million patients, required hospitalization.

Common reasons for hospitalization include need for close monitoring due to existing or expected clinical compromise, initiation of an intensive diagnostic workup, expected need for surgical procedures, and administration of treatments that are complex and technology intensive or have a high adverse effect profile.

In the traditional model of providing hospital care, the PCP admits the patient to the hospital and continues to personally direct the patient's care, examining the patient while on rounds in the hospital daily; writing all orders for diagnostic studies, medications, and other care; and consulting directly with subspecialists as needed. Due to economic and structural pressures from a changing health care system, a second model has emerged in which, once the PCP admits the patient to the hospital, further care is coordinated by a pediatrician specializing in inpatient medicine: a hospitalist.

The term *hospitalist* was first coined by Wachter and Goldman in 1996. Although hospitalists existed prior to that time, the prevalence of hospitalists has increased significantly in the decades since. The Society of Hospital Medicine defines the scope of the hospitalist's work to include the clinical care of acutely ill, hospitalized patients; education, research, and leadership in the field of hospital medicine; and working to enhance the performance of hospitals and health care systems.

While hospitalists are unable to provide the uninterrupted continuity of care that PCPs provide in the traditional model, hospitalist systems offer a different advantage: the extended physical presence of a physician in the hospital who is responsible for the patient's care—as much as 24 hours a day, 7 days a week in some systems—which is impossible to sustain for a PCP with a busy outpatient practice.

Inpatient Pediatric Care

Every patient presenting for admission to the hospital requires a thorough initial evaluation (history and physical examination) following a direct verbal handoff from the health professional requesting the patient be admitted. If admission is requested by someone other than the PCP (eg, emergency physician, surgeon following a surgical procedure), the hospitalist should consider contacting the PCP to establish a relationship, gather more information about the presenting symptom, and learn more about the patient's established medical problems and routine care. Primary care physicians may not always be available, and, as such, it is helpful if patients have been thoroughly educated on their medical conditions and carry a list of their medications and allergies with them.

Inpatient pediatric care should be *patient and family centered,* which has been defined by the American Academy of Pediatrics as "health care that is grounded in a mutually beneficial partnership among patients, families, and providers that recognizes the importance of the family in the patient's life." In the hospital setting, this may take the form of *multidisciplinary family-centered*

rounds, a system in which doctors, nurses, and other allied health professionals make rounds together on hospitalized patients with their families at the bedside. During rounds, health professionals educate patients and families, hear their preferences, and include them in the medical decision making process. Some families may prefer not to participate in rounds, and this preference should be respected as well. If there is a language barrier, in-person, video, or telephonic interpreters should be used to facilitate making rounds, in accordance with the principle of equitability of care. A *child life specialist* may be consulted to help the patient cope with the hospitalization, including daily rounds and anxiety-provoking or painful procedures, by clarifying what is discussed in terms the child can understand and helping the child process or be distracted from these events through various types of creative play.

Patient- and family-centered care is complemented by the application of *evidence-based medicine* principles to medical decision-making. Questions of diagnosis, prognosis, treatment, or avoidance of harm should be clearly defined to facilitate an effective review of the medical literature. One way of developing a focused clinical question is through the PICO process, wherein the physician identifies the applicable *p*atient population, the *i*ntervention (ie, treatment, diagnostic test, or prognostic factor), the *c*omparison (ie, control or placebo group), and the *o*utcome (ie, diagnosis, prognosis, or harm to the patient). For example, in formulating a diagnostic workup for a 5-year-old patient presenting with an asthma exacerbation, the physician might ask whether school-age children with asthma (P) who undergo chest radiography (I) have a shorter length of hospital stay (O) than children who undergo no imaging (C).

Advances in technology have made it possible to consult medical evidence at the point of care—even in the patient's room during bedside rounds—with the use of laptops, tablets, and in-room computers. When searching through primary research studies, such as randomized controlled trials, to answer a clinical question, the physician must determine whether the results are valid and generalizable to the patient under consideration. It may be more efficient and just as legitimate to use a summary of the evidence, such as a systematic review, which may be available through an established medical journal or a web-based service. Having the PCP as an ally during the hospital stay may give the hospitalist more insight into how applicable a certain study is to the patient for whom the hospitalist is caring.

Hospitalists should also make use of clinical practice guidelines as a way of providing standardized and evidence-based care. The Health and Medicine Division of the National Academies (formerly known as the Institute of Medicine) defines *clinical practice guidelines* as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options." In applying clinical practice guidelines, hospitalists should consider factors specific to the individual patient, such as comorbid conditions, limited availability of services in specific hospital settings, and patient values and preferences, that may warrant deviating from aspects of care recommended by the guidelines. Many of the guidelines used by hospitalists include discharge criteria, which are often dependent on availability of outpatient follow-up. This is yet another example of importance of communication with PCPs throughout patient hospitalization.

In addition to providing routine inpatient care, some hospitalists also provide specialized care, such as procedural sedation, palliative care consultations, and surgical or medical comanagement. Hospitalists often play a role in accepting patients for admission to the inpatient service, facilitating hospital-to-hospital transfers, and providing physician-assisted transport. They may also be tasked with determining the appropriate mode and level of transport.

Due to medical and technological advances leading to improved survival rates, hospitalists are increasingly caring for the growing population of children with complex medical needs. Providing quality care to these children is challenging due to their dependence on medical technologies and multiple medications, the paucity of applicable clinical evidence to support management strategies, and the need for time-intensive and complex care coordination. Depending on the resources available to the family and the PCP's familiarity with the patient (which may be limited if the patient has had frequent or prolonged hospital stays), transitioning the patient to the outpatient medical home may be particularly challenging. Specific efforts should be made to ensure a quality handoff so that there are no lapses in care and the PCP fully understands any adjustments made to the care plan during hospitalization.

Patient Safety and Quality Improvement

While it is important for individual physicians to engage in clinical practice that is family centered and evidence based, the next step is to ensure that quality care is being systematically delivered at the hospital level, and where it is not, that quality improvement (QI) programs are initiated. In its 2001 report, *Crossing the Quality Chasm,* the Institute of Medicine defined quality health care as having 6 characteristics: safe, effective, efficient, patient centered, timely, and equitable. Opportunities to improve the quality of care delivered by the hospital may be suggested by issues faced in individual patient encounters, quality metrics tracked by hospital administration (eg, length of stay, readmissions), or feedback from patients, their families, and their PCPs.

One model for the creation of QI projects is the *Plan-Do-Study-Act* cycle. In the Plan phase, the hospitalist identifies a problem or aim, defines a change that could be made to address the problem, and determines how the effectiveness of the change will be measured. It is usually necessary to form a team of like-minded physicians, administrators, nurses, and other allied health professionals early in the planning process. In the Do phase, the change is implemented, and data are collected about its effectiveness. These data may include *process measures* (ie, how

consistently the change is implemented) and *outcome measures* (ie, the effect of the change on the patient population, hospital system, costs). In the Study phase, data are analyzed, and successes and failures of the program are identified. Finally, in the Act phase, the team determines whether the change should be continued and adopted more widely in the hospital, modified in some way, or discarded altogether. Depending on the project, additional Plan-Do-Study-Act cycles may be needed to maximize the breadth and depth of the effect. Successes should be shared publicly with the hospital community to promote support for further QI efforts.

Physicians should also promote a *culture of safety* in the hospital, meaning that the hospital's processes and workforce are dedicated to the promotion of patient safety. *Adverse events,* a term encompassing all injuries caused by medical management, are common and are often caused by preventable medical errors, especially medication errors (eg, incorrect dosing, administering medications to the wrong patient). Common initiatives to improve patient safety include use of electronic health records and computerized order entry, review of orders by multiple health professionals, promotion of sterile technique and handwashing, work-hour limitations to prevent fatigue, and having time-outs before procedures to verify the patient's identity and the site of the procedure. Hospitals should hold regular morbidity and mortality conferences to review cases in which adverse events occur. These conferences should be confidential and focus not on blaming individual health professionals but on identifying systemic failures that may be corrected to prevent future adverse events. When adverse events occur, patients and their families should be informed in a timely fashion, according to procedures established by the hospital.

Transitions of Care

Inpatient systems in which hospitalists work in shifts typically have physician-to-physician handoffs of patient care responsibility at least once every 24 hours. Resident work hours in teaching hospitals have been limited to promote patient safety, but this also results in more frequent patient handoffs. If there is inadequate communication, handoffs may increase risk for medical errors and adverse events. Safe handoffs may be promoted by written handoff notes and strategies for effective verbal handoffs. One such strategy uses the I-PASS mnemonic, with the letters standing for a 5-step process in verbal handoffs (Box 19.1).

The discharge process should begin as soon as the patient is hospitalized. Goals of the hospitalization, discharge criteria, potential barriers to discharge, and an anticipated date of discharge should be identified in concert with the patient and family and reviewed during daily rounds. The hospitalist should formulate the discharge plan together with the other health care and allied health professionals involved in the care of the patient, including subspecialists, nurses, social workers, and discharge planners. For patients with complex needs, issues to address may include procurement of durable medical equipment, insurance coverage for medications, scheduling of follow-up appointments, and provision of other services, such as in-home nursing. The use of written or computerized discharge checklists may help ensure that no element is delayed long enough to prolong the hospital stay or forgotten altogether.

Box 19.1. I-PASS Mnemonic for Verbal Handoffs

- Illness severity (ie, stable or unstable)
- Patient summary (ie, summary statement, events leading up to admission, hospital course, ongoing assessment, plan)
- Action list (ie, to-do list, timeline, ownership)
- Situation awareness and contingency planning (ie, know what's going on and plan for what might happen)
- Synthesis by receiver (ie, receiver summarizes what was heard, asks questions, and restates key action items)

The final result of the discharge process is the transition of care from the hospitalist back to the PCP and medical home. If communication is poor, this transition carries with it the potential for significant information loss (eg, the hospital course, new diagnoses, future outpatient care needs such as subspecialty referrals and laboratory testing) and resulting adverse events for the patient. Ideally, the hospitalist should strive to communicate periodically with the PCP throughout the hospitalization, especially at the time of any important events. Most essential is communication at the time of discharge, which may take the form of verbal updates by telephone, emailed updates, and faxing or emailing of discharge summaries.

Education

A large portion of pediatric residency training occurs on inpatient units, and hospitalists are at the front line of pediatric resident education. When leading traditional resident-covered inpatient teams, hospitalists may contribute added educational value through direct observation of trainee history taking and physical examination skills, providing frequent and effective feedback, and promoting trainee autonomy on family-centered rounds. Due to resident duty hour restrictions, hospitalists are increasingly providing direct patient care on services without residents or other trainees, and many hospitalists practice in community hospitals without training programs. In these cases, there may be opportunities to educate non-pediatrician physicians (eg, surgeons, emergency physicians), nurse practitioners, and physician assistants in topics related to pediatric care.

Conclusion

The use of hospitalists to provide inpatient pediatric care has been on the rise over the past 2 decades since the term was first introduced. Studies of hospitalist systems suggest that the quality of care provided by hospitalists is equivalent to, and in some ways may improve on, care delivered via the traditional model. When attention is paid to maintaining communication, hospitalists have the potential to be partners in care with PCPs and the outpatient medical home.

CASE RESOLUTION

The patient is admitted to a monitored bed, and, after the initial assessment, the hospitalist concurs with the diagnosis of bronchiolitis. Based on current clinical practice guidelines, the hospitalist discontinues the use of systemic steroids and bronchodilators. The hospitalist obtains the number of the PCP from the family and places a call on the day of admission; during the call, the hospitalist learns that the patient has a penicillin allergy that was not reported by the parents during the history and physical examination. The hospitalist also begins to explore the possibility of initiating a quality improvement project in the management of bronchiolitis, which would use the clinical practice guidelines to create a set protocol for admissions with an order template in the electronic health record. The patient improves over the subsequent 3 days and is transitioned off oxygen. The hospitalist, together with a discharge planner, reconnects with the PCP, faxes a discharge summary, and arranges a follow-up appointment 3 days after discharge at a time when the parents are available. The patient is seen by the PCP at the scheduled appointment time. The parents tell the PCP they were told to monitor her respiratory effort, oral fluid intake, and urine output, all of which have been normal. While the parents have noticed that she still has a runny nose and cough, these symptoms have improved since discharge from the hospital.

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CHAPTER 20

Pediatric Genomic Medicine

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CASE STUDY

A 4-year-old boy with moderate global developmental delay is brought to his pediatrician's office for evaluation. The patient has an unremarkable family history and normal physical examination findings. Previous evaluation included normal karyotype and fragile X syndrome DNA test results. The patient's parents would like to know whether there is anything else that can be done to determine the etiology of the delay. In addition, his mother has recently read about companies that offer multiple genetic tests to consumers and wonders whether these tests will be useful as well.

Questions

1. What is microarray technology, and how is it useful in pediatric practice?
2. How is next-generation sequencing technology affecting current practice?
3. What are the limitations of these new technologies?
4. What is direct-to-consumer genetic testing?

The National Human Genome Research Institute at the National Institutes of Health describes genomic medicine as the incorporation of an individual's genomic information into clinical care. In this way, care involves diagnosis, therapeutic decision-making, health outcomes, and policy implications. The Human Genome Project (HGP) was an extensive, broad-based, and multidisciplinary research effort to develop knowledge of biology and disease—leading to the potential for so-called precision medicine, based on genome sequence information. The first essentially complete human sequence was published in 2003. The cost of sequencing a human genome has decreased from approximately $100 million in 2003 to about $1,000 in 2018, according to National Human Genome Research Institute data.

Whole exome sequencing (WES) uses next-generation sequencing to focus on exons, the regions of the genome that contain the actual DNA code for making proteins. Overall, the exons amount to about 1.5% of the human genome. Whole exome sequencing costs less than whole genome sequencing, and the functional significance of variants within exons is easier to interpret. Whole exome sequencing or whole genome sequencing is an appropriate study when a single-gene (or mendelian) disorder is suspected.

Chromosomal microarray analysis—compared with standard chromosome analysis—dramatically increased diagnostic yields for patients with intellectual disability, autism spectrum disorder (ASD), and multiple congenital anomalies. Genetic testing via gene sequencing panels (eg, 20–1,000 genes) and WES have driven diagnostic yields still further. Direct-to-consumer genetic testing is also available, designed to provide information without physician input. Pharmacogenomics, which promises individualized drug therapy based on genomic data, is moving toward applications to common diseases.

Epidemiology: Human Genome Anatomy

Human cells have 2 haploid genomes (ie, 23 pairs of chromosomes, 1 pair of most genes), each containing 3 billion base pairs with an estimated 20,000 to 25,000 protein-encoding genes, plus a variable number of copies of the mitochondrial genome. On average, 2 humans share 99.9% of their DNA. There are at least 10 million single nucleotide polymorphisms (SNPs), which are single base changes that are present in a substantial percentage of the population (>1%). A small percentage of SNPs fall within known coding or regulatory regions of genes and directly influence gene function. The remaining SNPs may have unclear effects on gene function, but they may be inherited in recognizable patterns (haplotypes) with other SNPs.

Recently, it has become evident that most human DNA variation is not represented by SNPs. Instead, copy number variants, in which DNA segments containing up to several million base pairs are duplicated or deleted, account for a substantial portion of variation among individuals. Approximately 12% of the genome can exhibit copy number variation, but the effect of such variation on individual phenotypes is unknown.

Autosomal recessive disorders are caused by pathogenic variants in each of the 2 copies of a disease-associated gene. Carriers of such disorders, with only 1 variant or disease allele, are typically asymptomatic. Although most autosomal recessive disorders are rare, most humans are carriers of several different recessive disease alleles. In a 2011 study, an average of 2.8 recessive variants was observed per person, among 448 genes involved in severe autosomal recessive disorders.

Pathophysiology: Genotype and Phenotype Correlations and Environment

Genomic data provide information about the genes on which pathogenic mutations are found. But many diseases are caused by a combination of genetic susceptibility and environmental factors. The first examples of such interactions were monogenic conditions, such as complement deficiency (which predisposes patients to bacterial meningitis) or mendelian cancer syndromes (which cause extreme radiation sensitivity). However, the gene-environment connection is now recognized to be more complex. For example, certain environmental conditions have been found to cause DNA methylation, a mechanism for gene silencing without changing the DNA sequence. These so-called epigenetic changes may persist across generations. As an example, mothers exposed to wartime famine may birth children who are predisposed to conservation of energy. When these children are fed a typical American diet, they are prone to development of obesity and diabetes. Also, fetal cells that persist in maternal circulation (fetal microchimerism) may play a role in tumor prevention and susceptibility to autoimmune disease. Finally, our bodies contain more bacteria than human cells, and the interaction of the bacterial and human genomes is thought to play an important role in the development of some diseases.

Clinical Presentation, History, and Physical Examination

A thorough history and physical examination will continue to be critical components of patient assessment in the genomic age of medicine. Large databases will be needed to correlate human genotypes with corresponding phenotypes defined by the patient's clinical presentation. Even when genetic and epigenetic sequencing is commonplace, the only way to measure the effect of the disease on the individual is by clinical assessment.

Laboratory Tests

Microarray testing, which includes a wide range of different technologies, has had a dramatic effect on the evaluation of common pediatric conditions, such as intellectual disability and ASD. Comparative genomic hybridization (CGH) microarray testing uses closely spaced DNA probes to detect chromosomal deletions or duplications at 100 to 10,000 times the resolution of standard karyotyping. The diagnostic yields for patients with intellectual disability and multiple congenital anomalies has increased from 3% to 4% to 15% to 20%, using this technology. For example, patients with ASD with normal karyotypes may have microdeletions or microduplications of 16p11.2. Several relatively common genetic conditions, such as 1p36 deletion syndrome, a form of severe intellectual disability that affects 1 in every 5,000 to 10,000 newborns, have been delineated through the use of microarray testing.

Single nucleotide polymorphism microarray testing has largely replaced CGH. It detects the same chromosomal imbalances as CGH, but SNP microarray testing can pinpoint regions of homozygosity, which represent identical sequences on both copies of a chromosome. The information may be useful to consanguineous couples, because it suggests areas where abnormal autosomal recessive disorder genes may be found. In addition, SNP microarray testing can detect some cases of uniparental isodisomy (inheritance of 2 identical copies of a chromosome from 1 parent) and may suggest the presence of an imprinting disorder, such as Prader-Willi syndrome.

Although microarray testing has largely replaced standard karyotyping, microarray testing cannot detect carriers of balanced translocation or patients with mosaicism (when the proportion of abnormal cells is <25%–30%). Some deletions or duplications detected by microarray testing are benign variants. Therefore, lack of availability of parental samples may hinder interpretation of an abnormal finding in a child.

Next-generation sequencing is a term used to describe methods for parallel sequencing of billions of base pairs at relatively low costs. Whole exome sequencing focuses on the 1% of the genome that encodes proteins and has been used for clinical testing in the past several years. A 2013 report shows a diagnostic yield of 25% for this technology in 250 samples studied. Whole genome sequencing has also become clinically available, although perhaps large-scale discovery of variation in regulatory elements located outside the coding regions has yet to be fully realized. These technologies have created a major paradigm shift, by decreasing the time to diagnosis and averting many costly and invasive procedures, such as muscle biopsy. Improvements in the technology and the bioinformatics used to interpret results are expected to increase the use of these tools.

Next-generation sequencing methods have certain limitations that should be addressed as technology progresses. Some genes, particularly those with high guanine-cytosine content, are not well captured or sequenced with current high-volume technologies. Exome sequencing cannot capture triplet repeat conditions, such as fragile X syndrome. Microduplications and microdeletions (of exons) are not normally detected with current technologies and must be assessed separately, using a microarray.

A patient's next-generation sequencing results will have thousands of differences from reference sequences. Bioinformatic algorithms must be used to sift through the data and determine the changes that are potentially relevant to the patient's condition. Parental testing often provides an essential reference but may not always be available. The testing laboratory classifies variants found into 5 categories: pathogenic, likely pathogenic, variants of unknown significance, likely benign, and benign. Family counseling may be limited for variants of unknown significance. Technology will drive down the price of sequencing over time, but the cost of bioinformatics will dominate the price of these new technologies as the amount of data increases.

Direct-to-Consumer Genetic Testing

Several commercial testing companies now market genetic tests directly to consumers. These tests purport to provide disease risk information by analyzing multiple SNPs along with common disease mutations. However, the tests may lack sensitivity and specificity, because analyses are based on limited genetic markers without

family history or phenotype information. Many consumers (and their physicians) are ill-equipped to understand the results, and patients of color may have indeterminate results. These companies argue that consumers have the right to know their genetic information, and some offer genetic counseling services. In 2010, the US Food and Drug Administration decided to develop regulations for the sale of direct-to-consumer genetic tests.

Management: Pharmacogenomics

Individualized pharmacological treatment has always been 1 of the goals of the HGP. Although pharmacogenomics is a fairly young field, several tests are available that can reduce the risk of an adverse drug reaction. Patients with variant thiopurine methyltransferase alleles may experience severe toxicity to azathioprine and 6-mercaptopurine. Children with a 1555A>G mutation in the mitochondrial genome are susceptible to aminoglycoside-induced hearing loss, even after a single dose of an aminoglycoside antibiotic. Pharmacogenomic treatment of common diseases (eg, asthma) is an active area of investigation and may allow for a more rational choice of drug regimens.

Future Developments

The huge potential of the HGP now influences several areas of medicine, including pediatrics. During the next decade, genomics will likely continue to revolutionize the diagnosis of rare or previously uncharacterized mendelian disorders. The impact of genes on common diseases, such as atherosclerosis, is being investigated through ever larger genome-wide association studies and polygenic risk scores. Although molecular diagnoses of previously unidentified diseases have increased over the past several years, our understanding of disease pathogenesis and treatment has not kept pace with the explosion in information. It is unclear how individuals will use genomic information to improve health—whether by altering lifestyles or by use of precision drugs, or both.

In addition, whole exome and whole genome sequencing create various ethical issues. If a patient presents with heart disease and testing shows an increased risk for Alzheimer disease, should this information be returned to the patient? It is certain that pediatricians will need to familiarize themselves with genomic medicine, because the number of tests—and patients seeking testing—will exceed the availability of medical genetics specialists.

Glossary	
Autism spectrum disorder	A medical condition resulting in deficits in social communication and social interaction and characterized by restricted, repeated interests and behaviors starting in early childhood. Other formal criteria are also used to establish a diagnosis.
Comparative genomic hybridization	A chromosomal microarray method in which tens of thousands of DNA probes for regions along the genome can be used to detect chromosome deletions or duplications at 100 to 10,000 times the resolution of standard karyotyping. Comparative genomic hybridization has largely been replaced by single nucleotide polymorphism microarray methods. The DNA probes (for binding to patient DNA) are immobilized on glass slides—called *microarrays*.
Copy number variant	Variants in the structure of the genome having different numbers of copies of DNA segments (usually between 1 kilobase and 5 megabases long). Copy number variants form a large part of human DNA diversity, including causes of some genetic conditions.
Human Genome Project	The worldwide effort to determine the DNA sequence of the *Homo sapiens* genome (3 billion bases). The project was launched in the United States by the US Department of Energy and the National Institutes of Health. Efforts were also started in France, the United Kingdom, and Japan. Other countries joined later (eg, Germany, China). The project ran from approximately 1988 to 2003. A review of the effort stated: "For everyone, this achievement represents a major turning point in our quest to learn how all the components of the human genome interact and contribute to biological processes and physiological complexity."
National Human Genome Research Institute	One of the 27 institutes and centers of the National Institutes of Health. It was established in 1989 and is "devoted to advancing health through genome research."
Single nucleotide polymorphism	The most common and simplest type of DNA polymorphism, in which 1 base is changed to another. These polymorphisms occur roughly every 1,000 base pairs in the genome. Those that occur in or around genes may change the amino acid sequence of the encoded protein, may produce or remove a stop codon, may impair the usual processing (splicing) of the messenger RNA, may change how the gene is controlled, or may have no effect at all.
Single nucleotide polymorphism (SNP) microarray testing	A chromosomal microarray method that has largely replaced comparative genomic hybridization. It may contain a few million oligonucleotide probes (approximately 25 nucleotides long) for regions along the genome. In addition to detecting chromosome deletions and duplications, SNP microarray testing can also detect long regions of homozygosity, indicating uniparental disomy or consanguinity. The diagnostic utility of chromosomal microarray testing among children with intellectual disability, autism spectrum disorder, and congenital anomalies has been estimated to be 10% to 20%.
Whole exome sequencing (WES)	Sequencing all the known coding regions in the genome. The diagnostic utility of WES among children with intellectual disability, autism spectrum disorder, and congenital anomalies has been estimated to be at least 30% to 40%.

CASE RESOLUTION

The patient's microarray testing results show a small microdeletion in chromosome 6. Parental testing indicates that the microdeletion is present in the patient's father, who has had normal development. Further testing includes WES, which shows a potential missense mutation in *CASK*, a gene on the X chromosome that may cause developmental delay. This alteration is not found in the patient's mother, implying that it is most likely deleterious. The parents receive genetic counseling about future pregnancies.

Resource

National Human Genome Research Institute "The Human Genome Project"
www.genome.gov/10001772

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CHAPTER 21

Principles of Quality Improvement: Improving Health Care for Pediatric Patients

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CASE STUDY

During a routine staff meeting at your group pediatric practice, it was noted that many of the patients cared for by your practice are behind in their immunizations. The reasons for this are unclear, because you and your colleagues are strong proponents of the timely administration of preventive immunizations. You want to develop a mechanism to determine what factors are resulting in delayed vaccine administration.

Questions

1. What is quality improvement?
2. How does assessing the delivery of recommended health maintenance relate to quality?
3. How is the prevention of medical errors related to quality improvement?
4. What is the difference between harm and error?
5. What factors are associated with medical errors?
6. What is meant by organizational culture?

History

The origin of medical quality improvement (QI) lies not in medicine but in industry and dates to the 1920s. Walter A. Shewhart, PhD, was an American physicist, engineer, and statistician. In 1924, Shewhart presented a memo in which he showed a schematic control chart. The diagram and text set forth all the essential principles and considerations involved in quality control. Shewhart pointed out the importance of reducing variation in a manufacturing process and noted that continual process adjustment in reaction to nonconformance actually increased variation and degraded quality. He went on to develop *data presentation rules* that remain important today: Data have no meaning apart from their context, and data contain signal and noise. To be able to extract information, it is imperative to separate the signal from the noise within the data.

In the 1950s, Shewhart's colleague, W. Edwards Deming, PhD, while working in Japan, taught top management how to improve design and, subsequently, service, product quality, testing, and sales. Deming, applying Shewhart's concepts, described the Plan-Do-Study-Act (PDSA) method as an approach to QI. He opined, "The key is to practice continual improvement and think of manufacturing as a system, not as bits and pieces."

In the 1970s, physician Avedis Donabedian, MD, MPH, proposed a model for assessing health care quality by describing 7 pillars of quality (Box 21.1). He posited that structure is the environment in which health care is provided, process is the method by which health care is provided, and outcome is the result of the care provided. He emphasized the importance of measurement and evaluation of health care quality, ensuring completeness and accuracy of medical records, observer bias, patient satisfaction, and cultural preferences for health care.

In 1991, Paul B. Batalden, MD, and Donald M. Berwick, MD, MPP, FRCP, helped found the Institute for Healthcare Improvement (IHI), which has resulted in the application of QI science to health care both in the United States and internationally. The IHI promotes the adoption of measurement and feedback to improve the quality of health care. The IHI is an easily accessible resource for education and information related to QI in health care.

Historically, QI efforts were focused on "quality assurance." The goal was to minimize "defects" as measured by audits. Currently,

Box 21.1. The Seven Pillars of Quality

- Efficacy
- Efficiency
- Optimality
- Acceptability
- Legitimacy
- Equity
- Cost

the emphasis is on QI, which focuses on moving the entire performance curve toward a higher level of performance by identifying and adopting best practices rather than simply focusing on low performers. Ongoing measurement is vital to sustaining any improvement. The process of QI requires careful planning, thorough documentation, consistent analysis, and open-mindedness to results. In health care, QI consists of systematic and continuous actions that result in a measurable improvement in health care services and the health status of the targeted patient group.

Quality Improvement in Pediatrics

Quality improvement works to strengthen systems and processes and, in medicine, focuses on patients and the use of data to drive improvement in patient safety and health care. To achieve a different level of performance and improve quality, an organization must be willing to change.

The specialty of pediatrics emphasizes health maintenance and disease prevention. Studies have shown that recommended targets are not being consistently realized, however. Mangione-Smith et al reported that children received only 46.5% of recommended care for preventive services, acute illness management, and ongoing care of chronic conditions. In 2017, as reported by the Centers for Disease Control and Prevention, this number had not changed. Shaughnessy and Nickel reported that 21% of outpatient prescriptions in a family medicine practice contained at least 1 error. Other investigators found that medication samples were dispensed with inadequate documentation. In a pediatric emergency department in Canada, 100 prescribing errors and 39 medication administration errors occurred per 1,000 patients. In a sample of new prescriptions for 22 common medications in outpatient pediatric clinics, approximately 15% were dispensed with potential dosing errors. Even with the use of electronic medical records and e-prescribing technology, prescribing errors continue to occur as the result of auto-populate errors and/or choosing the wrong medications and/or wrong formulations from the drop-down menus. Multiple medication alerts during the prescribing task distract the clinician, resulting in errors. In addition, these frequent and often irrelevant alerts may cause "alert fatigue." Outdated or incorrect information, such as weight entered as pounds rather than kilograms into the electronic medical records also may result in dosing errors.

The Learning from Errors in Ambulatory Pediatrics study aimed to learn the scope of, range of, potential causes of, and possible solutions to medical errors in pediatric ambulatory care. The study found that among 14 pediatric practice sites, 147 medical errors were reported during the 4-month study period. The largest group of errors was related to medical treatment (37%). Of the medical treatment errors, 85% were medication errors. Errors also were associated with patient identification (22%); preventive care, including immunizations (15%); diagnostic testing (13%); and patient communication (8%). According to the Medical Professional Liability Association (formerly the Physician Insurers Association of America), from 2003 through 2012 diagnostic errors accounted for 828 closed pediatric cases, with an average indemnity of $414,455, and medication errors accounted for 113 closed cases, with an average indemnity of $207,916. According to a systematic review, as many as 10% of all pediatric medication orders result in a medication error.

Many examples exist of errors in inpatient care as well. A study of inpatient medication errors found that among 1,000 children in 12 independent children's hospitals, 1 in 15 children was exposed to wrong medications, side effects, or drug interactions. Takata and Currier reported a rate of 11.1 adverse events per 100 pediatric inpatients; 22% of these errors were deemed preventable. In a 2014 report from The Joint Commission, the root causes of more than 80% of almost 2,400 sentinel events were human factors (eg, staff supervision issues), leadership (eg, organizational planning), communication (eg, with patients or administrators) and assessment, including timing and/or scope.

Kurtin and Stucky describe 5 barriers or challenges to high-quality care in the pediatric and adult health arenas, the first of which is widespread unnecessary variation in care (Table 21.1). To prevent medical error, it is necessary to understand how, when, and where it occurs; evaluate the system that allowed the error to happen; and keep the system open and blame-free (Box 21.2).

Factors associated with risk of error are not the individuals who work in the system but rather the system in which the individuals work. To reduce the risk of error, the language of patient safety must be understood by all health professionals, and a deeper understanding of the principles of systems analysis work models and other solutions must be developed.

Definitions

Understanding QI and improving patient safety requires familiarity with the terminology. The National Patient Safety Foundation defines *patient safety* as the avoidance, prevention, and amelioration of adverse outcomes or injuries stemming from the processes of health care. The Health and Medicine Division of the National Academies (formerly the Institute of Medicine [IOM]) defines *patient safety* as freedom from accidental injury.

An *adverse event* is injury caused by medical management rather than by an underlying condition. Some adverse events are not preventable. One example of a non-preventable adverse event is the patient who receives the appropriate antibiotic at the appropriate

Table 21.1. Barriers to High-quality Health Care

Barrier	*Explanation*
Unnecessary variation in care	Diagnostic or therapeutic interventions performed at the discretion of the ordering physician and not required by the patient's condition
Gap between knowledge and practice	The time—perhaps many years—from publication of a proven new practice in the medical literature to its use in routine clinical care
Failure of physicians to understand and work in the hospital's complex systems of care	Challenges to accessing information, data, personnel, and/or materials to facilitate patient care
Need to improve patient safety	No consistent mechanism in place
Slow adoption and routine use of practices that can improve clinical outcomes and patient safety	May be mitigated by the use of clinical pathways

Box 21.2. Factors Associated With Errors in Health Care

- Communication failure
- Frequent distractions and interruptions
- Inadequate supervision
- Medication issues
- Limited access to patient information
- Noisy work environment
- Lack of 24-hour pediatric pharmacy
- Emergency situations

time in an appropriate dose and who has an allergic reaction to the medication because of the existence of an allergy that was unknown to both the patient and the staff. This differs from *medical error*, which is the failure of a planned action to be completed as intended (ie, error in execution) or the use of a wrong plan to achieve an aim (ie, error of planning). *Outcomes* summarize the effectiveness of care, including adverse events.

James Reason, who did extensive work on organization models of accidents, further delineates the terminology. A *slip* is an error in execution, that is, the observable action deviates from what was planned. A *lapse* is an error in execution resulting from a memory failure. A *mistake* is a knowledge-based failure, that is, the plan was performed correctly, but the planned action was wrong for the situation. An *active error* (ie, sharp-end error) typically occurs in a patient care area by a frontline practitioner; the effects may be felt immediately. A *latent error* (ie, blunt error) is the result of a systems-based problem and may relate to poor design, incorrect installation, look-alike packaging, soundalike names, faulty maintenance, or bad management decisions. Latent errors are more difficult to identify and hard to recognize. Health care workers frequently develop work-arounds to bypass the problem, which often leads to the belief that the work-around is normal.

A *system* is a set of interdependent human and nonhuman elements that interact to achieve a common aim. In a hospital, a system may be a unit or a department. *Processes* are the means by which care is delivered. Questions related to process include the following: Are policies routinely followed? Are evidence-based medicine guidelines implemented? Does the transfer of patients occur in an organized manner? *Work models* provide a conceptual framework for investigating events and processes to ensure the evaluation of all contributing factors. The PDSA method is an example of a conceptual framework. The premise of all work models is that an organized, systematic approach to event investigation results in reliable data that may be used to develop a new system.

Continuous QI (CQI) is the continued process of reviewing and improving processes and procedures associated with providing goods or services. A CQI approach may involve evaluating structure, process, or outcome either individually or—because of the considerable overlap that exists between the components and quality of care—as a whole.

When evaluating the quality of health by comparing outcomes, it is important to understand the concept of *risk adjustment*, which allows statistical adjustment of patient differences (eg, severity of illness) to make comparisons of outcomes clinically meaningful. Use of risk adjustment enables the translation of statistically significant tests into clinically meaningful results.

Errors and How They Occur

The pervasiveness of the medical error problem is enormous. In 1999, the IOM published *To Err Is Human: Building a Safer Health System*, in which it was reported that medical error accounted for approximately 44,000 to 98,000 deaths annually in US hospitals. This is more deaths than from AIDS, motor vehicle crashes, or breast cancer. The types of errors included adverse drug events, improper transfusions, surgical injuries, wrong-site surgeries, mistaken patient identity, and failure to prevent patient suicides. Most errors occurred in intensive care units, operating rooms, and emergency departments. The annual total cost of these errors was estimated to be between $17 billion and $29 billion. The cost of additional care was $8 billion. This figure does not account for lost income and productivity. A 2004 report of inpatient deaths estimated that 575,000 deaths were caused by medical error between 2000 and 2002, approximately 195,000 deaths per year. In 2008, the US Department of Health and Human Services Office of Inspector General reported 180,000 deaths per year resulting from medical error among Medicare beneficiaries alone.

The IOM made many recommendations in their report, including a balanced approach between regulatory and market-based initiatives as well as the establishment of a national focus to create

leadership, research, tools, and protocols to enhance the knowledge base about safety. It recommended raising performance standards and expectations for improvements in safety through the actions of oversight organizations, professional groups, and group purchasers of health care. An additional recommendation was to implement safety systems in health care organizations to ensure safe practices at the delivery level.

In 2001, the IOM published a follow-up report, *Crossing the Quality Chasm: A New Health System for the 21st Century.* Safety was deemed the key dimension of quality. The report also indicated that only a systems approach would work to improve quality in health care; trying harder is an inadequate approach. Per the report, a stepwise correction of problems in the system is the key to success. Additionally, it indicated a need to overcome the culture of blame, because human error is to be expected. Table 21.2 defines types of errors in health care.

Typically, medical errors are neither isolated events, nor are they made by a single person. Normally, numerous safe points and double checks are built into the process; however, each layer of safety has gaps or holes. When these gaps align, the error reaches the patient. Standardized approaches can reduce variability and improve system efficiency. The goal is to make the gaps as small as possible or even eradicate them. Many factors are associated with medical error, including human factors triggered by interruptions, fatigue, time pressures, anger, anxiety, fear, and boredom. Mistakes can result from a wrong plan of action. Mistakes may involve misinterpretation of a problem, lack of knowledge, and habitual patterns of thought. A *violation* is a purposeful rule violation, whether reasoned or reckless. The factors associated with risk are not the individuals who work in the system but rather the system in which the individuals work.

Harm Versus Error

The ultimate goal of QI is to reduce patient harm. Early QI efforts targeted the elimination of error in the belief that reducing error would decrease harm. This is not true, however; most medical errors never harm patients and may be clinically insignificant (eg, 1-hour delay in administration of acetaminophen). So why does one differentiate? Focusing on harm puts the microscope on the system, not the individual.

Table 21.2. Types of Errors in Health Care

Error	*Definition*
Diagnosis	Delayed diagnosis: failure to use indicated tests, use of outmoded tests or therapy, or failure to act on results of monitoring or tests
Treatment	Error in the performance of an operation, procedure, or test; an avoidable delay in treatment or failing to respond to an abnormal test; inappropriate/not indicated care
Medication	The most frequent type of error, which includes error in the dose; method of using a drug
Prevention	Failure to provide prophylactic treatment, or inadequate patient monitoring or treatment follow-up

Quality Improvement and Organizational Culture

"This is the way we do things around here."

Patients expect to receive quality health care without experiencing preventable harm. The IOM defined *quality* in health care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." One factor that influences quality in health care is organizational culture.

Many pediatricians are never taught about organizational culture. It is the invisible, powerful dictator of how things are done in an organization. Organizational culture is a latent and often unconscious set of forces that determines individual and collective behavior, ways of perceiving, thought patterns, and values. Hospitals have their own cultures. Subcultures exist among physicians and nurses as well as within departments (eg, critical care). It may be challenging to understand all the different subcultures within a hospital.

Activities or processes within a health care organization contain 2 major components: what is done (ie, what care is provided) and how it is done (ie, when, where, and by whom). Quality improvement can be achieved by addressing either component, but addressing both simultaneously has the greatest effect on QI. The goal of QI is to enable an organization to achieve the ideal critical pathway, which is one that allows proactive and efficient interaction between the care team and patient to achieve optimal health outcomes.

Promoting change is rarely easy. Some people may adapt and change appropriately, while others resist and become dysfunctional. Making changes requires an environment in which teamwork can grow. Groupthink must be avoided. The term *groupthink* was coined by Yale psychologist Irving Janis, PhD; it is "a way of thinking that people may adopt when they are members of a cohesive or homogeneous group; in particular, a group whose members seek unanimity of thought to the point that they cannot consider alternative ideas." It can prevent critical thinking and debate. Without disagreement, creativity can be lost. Negative effects of groupthink include an illusion of invulnerability, insulated leaders who may be protected from contradictory evidence, and members who accept confirming data and reject data that fail to fit their views. Alternatives are not considered, and individuals with conflicting views are discounted or demonized. Talented leaders welcome diversity of thought and ideas. Leaders must empower team members to have open discussions and offer ideas.

Communication is a key component of organizational culture. *Communication* involves 2 parts: message and meaning. The message is stated; meaning is interpreted and may be interpreted differently by different people. Strategies to improve communication are legion, including methods for remaining calm in high-workload, high-stress situations. Other strategies include increased verbalization, verbalizations that relate to problem-solving, speaking in the first-person plural, readback, and coordinating tasks to the

right person's experience level. Good communication encourages input from team members. Offering positive feedback builds confidence, reduces stress, and clarifies ambiguities. Team evaluations provide input on how well team members are communicating with each other and the progression toward achieving team goals. Benchmarking against a similar team may provide valuable information. An outside consultant may be hired to observe the team and provide feedback. Internally, the use of informal, regular meetings to discuss the team's progress and provide debriefing sessions to discuss the team process may be constructive in moving the team toward its goals and ensuring effective communication. All teams experience team conflict at some point. Conflict occurs when people come together to resolve a problem, dialogue about care improvement, or discuss changing processes to improve care. Team conflict must be managed effectively so that issues can be resolved while still providing the highest-quality patient care.

Teamwork has been defined by numerous organizations. In 2003, the IOM defined *teamwork* by stating, "All health professionals should be educated to deliver patient-centered care as members of an interdisciplinary team, emphasizing evidence-based practice, QI approaches, and informatics." The IOM defined a *multidisciplinary team* as one in which members cooperate, communicate, and integrate care to ensure that patient care is continuous and reliable.

Measuring Quality

Data are the cornerstone of QI. Ideally, measurements should evolve from the Health and Medicine Division of the National Academies quality aims (Box 21.3). Improvement measures may not be sufficiently valid and reliable for public dissemination yet may still be useful for benchmarking, for identifying best practices, or as part of QI initiatives.

Adult measures may not be appropriate for pediatrics. Pediatrics is unique because of the heterogeneity of patients, including age, size, diagnoses, and treatment modalities, including medication dosing.

Measures must be reliable. *Reliability* is the capacity of the measure to perform similarly under stated conditions over time. In health care, reliability and precision are often used interchangeably. *Precision* is the capacity of a measurement process to reproduce its own outcome. To achieve precision, a reliable system requires clear and concise definitions of the data fields to be collected. An effective approach is to train data collectors. A robust method for data coding and entry is also required. Reliability must be intermittently assessed within and between observers over time to ensure consistency.

Box 21.3. National Academy of Medicine Quality Aims

- Safe
- Effective
- Patient-centered
- Timely
- Efficient
- Equitable

Measures must also be valid. A measure is *valid* if it adequately represents the attribute of interest. *Internal validity* is the soundness of the developed indicator. *External validity* is the capacity for application of the indicator to a broader population.

Measures must be feasible and usable. *Feasibility* is the capacity to gather measures. For a measure to be usable, the intended audience must be able to understand the findings and use them in an appropriate fashion. A measure is *usable* if it enables the uncovering of meaningful differences between groups.

Three types of measure are essential to QI: outcomes measures, process measures, and balancing measures.

1. Outcomes measures: Address how the health care services provided to patients affect their health, functional status, and satisfaction (eg, the percentage of patients who died as a result of surgery).
2. Process measures: Address the health care services provided to patients (eg, the percentage of patients whose hemoglobin A_{1C} level was measured in the past year).
3. Balancing measures: Evaluate unintended consequences or the stability of the system being changed in the project (eg, ensuring that readmission rates are not increasing as a result of reducing length of hospital stay).

A balanced set of measures for a QI effort should include at least 1 outcome, 1 process, and 1 balancing measure. After measures are identified, an organization determines its data collection frequency and sampling. More frequent data collection allows an organization to focus its QI efforts more aggressively.

Quality Improvement Models

After opportunities for performance improvement have been identified, changes can be made to the underlying system targeted for improvement. The use of QI models alone or in combination is an effective approach for categorizing potential changes in the organization's system and identifying changes that have worked in similar settings.

Multiple QI models exist. Both the Care Model and Lean methodology provide frameworks for improving patient care, whereas the Model for Improvement, the FADE (focus, analyze, develop, execute and evaluate) model, and Six Sigma focus on processes. There are 6 fundamental aspects of care identified in the *Care Model*, which creates a system that promotes high-quality disease and prevention management. It does this by supporting productive interactions between patients, who take an active part in their care, and health professionals, who have the necessary resources and expertise.

Lean defines value based on what the patient wants. It maps how the value flows to the patient and ensures the competency of the process by making it cost effective and time efficient.

The *Model for Improvement* focuses on questions to set the aim or organizational goal, establish measures, and select changes. It incorporates PDSA cycles to test changes on a small scale.

The *FADE model* is separated into 4 broad steps: (1) focus: define the process to be improved; (2) analyze: collect and analyze data; (3) develop: develop action plans for improvement; (4) execute: implement the action plans, and evaluate (ie, measure and monitor the system to ensure success).

Six Sigma is a measurement-based strategy for process improvement and problem reduction. It is completed through the application of the QI project and accomplished with the use of 2 Six Sigma models: DMAIC (define, measure, analyze, improve, control), which is designed for use in examining existing processes, and DMADV (define, measure, analyze, design, verify), which is used to develop new processes.

Error Metrics

Measuring harm is often done using occurrence reports, which identify 2% to 8% of all adverse events in an inpatient setting. These reports may be done with retrospective, concurrent, or trigger-based chart review. No standardized methods exist for reporting, investigating, or disseminating information related to preventable adverse events. Historically, the qualitative concept of patient safety has been translated into quantitative metrics. Three frameworks that have been used include measuring error, measuring patient injuries, and measuring risk.

Error-based patient safety metrics are premised on the idea that the goal of medicine is to successfully implement the correct plan of care. It is an attractive measure of assessing safety because many errors occur and are somewhat easy to find. Many problems exist with error metrics, however, because few measures of error represent the true rate.

Error rate = (identified errors)/(potential opportunities for that error to occur)

The numerator (identified errors) may be hard to obtain because with reported events, only the errors reported are known, rather than the actual number of occurrences. Thus, the error rate is nothing more than a rate of reporting.

Another modality that has been proposed to obtain the true numerator is chart review. The difficulty with chart review lies in the number of steps in the process—error occurs, each error is recognized by a health professional, the error is documented by a health professional, the chart is reviewed, the reviewer recognizes the event during the chart review, and the error is attributed correctly. Ethnographic study (ie, the direct observation of people) is subject to the same pitfalls.

Other confounders include hindsight bias. To effectively rectify problems, the correct understanding and attribution of events that created the error must occur. The retrospective analysis of error creates the potential for incorrect or simplistic identification of causes of events. Subsystem failures are difficult to identify as a contributing cause of an adverse event. The incorrect or inadequate attribution of causality creates the potential for misguided actions to "solve" the wrong problem.

Focusing solely on active errors leaves latent failures unrecognized and unaddressed, thus increasing the vulnerability of the entire system to adverse events. Identifying errors is important, but focusing solely on errors may lead to "the blame game." Trends may be a barometer for organizational culture as it relates to patient safety. Identified errors provide learning opportunities, thereby preventing harm to other patients.

Injury-based patient safety metrics focus on unintended outcomes, such as catheter-related bloodstream infection, ventilator-associated pneumonia, in-hospital cardiac arrest, and death. Improvement efforts are more likely to focus on system vulnerabilities with a high potential for adverse events.

Risk-based patient safety metrics are a means of measuring hazards or risks. From a systems-based view, errors and injuries are the result of hazards or risks within the system of care. The focus is on hazardous conditions that increase the likelihood of downstream errors. Efforts are centered on 3 core areas: systematic risk identification, risk assessment, and risk reduction and/or elimination. This approach is proactive and saves counting errors and injuries. The elimination of risk includes the substitution of less risky alternatives, the development of administrative controls, and individual protection. It incorporates information gathered from the front-line bedside practitioner. The focus on risk reduction may decrease the need to quantify error rates or injury prevalence. This requires a shift in thinking from counting errors and injuries to proactively identifying risk. The goal is to identify systems-level problems that may be amenable to QI efforts.

Patient Safety and Error Prevention

The Institute for Safe Medication Practices developed a rank order of error-reduction strategies ranging from most effective (ie, forcing functions and constraints) to least effective (ie, education and/or information). In between are strategies (from most to least effective), such as automation and computerization, standardization and protocols, checklists and double-check systems, and rules and policies.

Education and information dissemination are important and helpful in that they increase awareness. Lectures are quickly forgotten, however, and signs are often ignored. Education and information dissemination is the least effective means to prevent the occurrence of error. Rules and policies are required by several agencies. Although rules and policies are a good resource, they are not an effective means of preventing a specific event.

Checklists, double-check systems, and bundles are very effective when they are a routine part of practice, but they are not foolproof. The best example of a double-check system is the surgical sponge and instrument counts done at the end of a surgical case. Checklists and bundles are also being used for other procedures, such as central line placement. Standardization minimizes the risk of error, and protocols bring a standard approach to a clinical issue. Checklists, bundles, and standardization are designed to eliminate variation from practitioner to practitioner and patient to patient. Any remaining weak points are prone to the occurrence of error. Automation and computerization are 2 of the best means of preventing medical error; however, there is still a risk of data entry error. Forcing functions and

constraints is the best way to prevent error through the use of safeguards. In this manner, systems and products are engineered to be safer from the ground up.

Plan-Do-Study-Act cycles are 1 method of developing and implementing change that results in improved patient safety and quality of care. Plan-Do-Study-Act cycles force small-scale, stepwise thinking; enable the making of predictions; force thoughtful deliberation on the increased knowledge; and subsequently facilitate change. The use of small-scale change can result in rapid adaptation and implementation of change in various health care settings.

Conclusions

The key elements to changing a system are the will to do whatever it takes to make the change, the ideas on which to base the design of the new system, and the execution of the changes to the system. Change is difficult, but sustaining change is even more complex. Hardwired sustainability in a new system is imperative. The old way must be more difficult or inconvenient to perform than the new way. In health care, spreading improvements depends on key individuals, and the role of leadership is a factor that is critical to success. Leaders must inspire and communicate a shared vision; model the way; challenge the current process; stop accepting the status quo; and enable others by ensuring access to resources, training, and time. Successes must be celebrated.

CASE RESOLUTION

During your staff meeting, you decide to use a PDSA cycle to examine the organization's vaccine administration practice, identify barriers to timely vaccine administration, and develop a plan to ensure that vaccines are administered in a timely fashion.

Plan: The charts of all patients seen for routine care in the past 3 months are pulled. The charts are audited using a premade checklist to identify vaccines given, vaccines missed, and barriers to administration. After analyzing the data, it becomes clear that many opportunities for immunization were missed because of inability to get parental consent. This seemed to coincide with a television program that discussed increasing rates of autism spectrum disorder associated with vaccination.

Do: At your next routine staff meeting, you present the data to your colleagues. You recommend rebutting the television show with a fact sheet and a discussion between the physician and parents. Your colleagues agree to implement this change, because it is low cost and easy to put into practice.

Study: Three months after implementation, you collect data and discover fewer missed opportunities for immunization and that your program has had some success. Some parents are still resistant to immunizing their children for fear of autism spectrum disorder.

Act: You present the follow-up data to your colleagues, and they agree to continue to implement the current strategy. The decision is made to reexamine the data again in 3 months to determine whether the program continues to be effective.

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CHAPTER 22

Pediatric Palliative Care: Principles and Practice

Jori Bogetz, MD, FAAP, and Richard Goldstein, MD, FAAP

CASE STUDY

Jason is a 17-year-old boy with spastic quadriplegia, severe global developmental delay, seizures, dystonia, and cortical blindness who is supported by a tracheostomy but is not ventilator dependent. He was born at 24 weeks' gestation and had a turbulent neonatal course. Since leaving the intensive care unit at 6 months of age, he has lived at home, cared for by his family, a loyal home nursing team, and his primary care pediatrician. Medically he has been fairly stable, with only episodic respiratory infections and numerous orthopedic procedures. Over the past 2 years, however, he has spent substantially more time in the intensive care unit because of increasing respiratory fragility. With so many hospitalizations and so little time feeling well at home, his parents have begun questioning whether the intensive medical care Jason receives translates into quality of life for him and his family.

Questions

1. What is pediatric palliative care, and how is it practiced?
2. What children receive palliative care, and what are the benefits and barriers to these services?
3. What are some of the essential considerations when communicating with families of seriously ill children?
4. How do children of different ages understand serious illness, death, and dying?
5. What role do primary care pediatricians have in the palliative care of their patients?

The Scope and Practice of Pediatric Palliative Care

Pediatricians develop deep, meaningful relationships with patients and their families. Mostly, patient care involves the typical ups and downs of childhood with acute pediatric illnesses. But some patients are challenged by a degree of illness that requires high levels of continuous medical management, care coordination, and advocacy. These children and their families live with significant uncertainty about the future and a "roller coaster" of health experiences that may even involve the child's death. Along with these difficulties, many pediatricians describe caring for children and families with serious illness as among the most rewarding aspects of their careers.

Palliative care is a framework that prioritizes the well-being of patients and families experiencing serious illness. This is accomplished through careful symptom management; attention to the medical, psychosocial, and spiritual needs of patients through multidisciplinary care; and establishing goals of care based on family-centered priorities. The American Academy of Pediatrics states that pediatric palliative care should be integrated starting at diagnosis and extending into hospice care and bereavement for any child with a serious illness. This care should be provided along with that provided by primary care pediatricians and in conjunction with community-based teams. These standards are illustrated in the *concurrent model* of palliative care, which is care that incorporates palliative care with disease-directed treatment throughout a child's illness and extends into bereavement (Figure 22.1). Despite its growing acceptance, palliative care is often incorrectly equated with end-of-life and hospice care. *Hospice* is a program of coordinated services offering comfort-centered care at the end of life in the home or community setting. Although hospice and palliative care have a shared philosophy and an overlap of many of the priorities of care, palliative care should not be considered only at the end of life, nor is it exclusive of curative or disease-directed care.

Palliative care is often thought of as a specialized area of practice. Subspecialty palliative care (ie, *secondary palliative care*) is practiced by health professionals with additional training who often provide education and advocacy in the field of palliative medicine and provide direct patient care in quite complex clinical situations. Important elements of palliative care can be practiced by other health professionals with trusted longitudinal relationships and tremendous insights into family dynamics and priorities, however. *Primary palliative care* is the term used to describe the palliative care provided by nonsubspecialty health professionals. It is the most fundamental form of palliative care that patients and their families receive. The skills of primary palliative care include the abilities to hold basic discussions about prognosis and goals of care, manage basic pain and symptoms, and address family and sibling issues

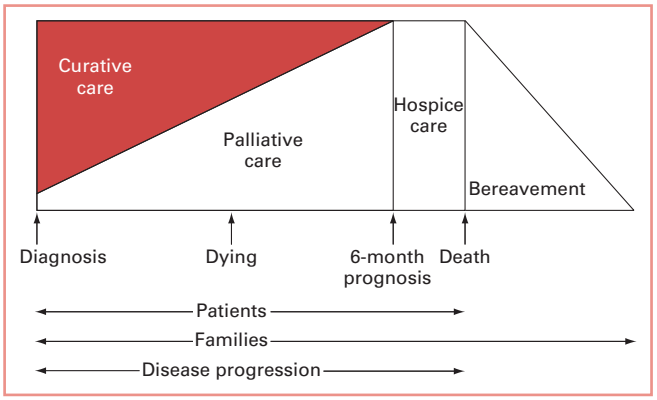

Figure 22.1. Integration of palliative care along with disease-directed treatments and continuing into bereavement.
Adapted with permission from Ferris FD, Balfour HM, Bowen K, et al. A model to guide patient and family care: based on nationally accepted principles and norms of practice. *J Pain Symptom Manage*. 2002 Aug;24(2):106-23.

that arise related to the illness course. Another important part of primary palliative care is the relationship that remains between the clinician and family after a child dies. Both primary and secondary palliative care are necessary in helping children and their families live as well as possible with serious illness.

Palliative care for children may be considered in the context of 4 major categories of serious illness: conditions for which curative treatment is possible but may fail (eg, cancer with a poor prognosis, complex congenital heart disease); conditions requiring intensive long-term treatment aimed at maintaining quality of life (eg, cystic fibrosis, muscular dystrophy); progressive conditions in which treatment is exclusively palliative after diagnosis (eg, Tay-Sachs disease, leukodystrophy); and conditions involving severe, nonprogressive disability, causing extreme vulnerability to health complications (eg, holoprosencephaly, extreme preterm birth with severe comorbidities). Many of these conditions are affected by medical advances and evolving clinical practices. The use of bone marrow transplant, gene therapy, and immunotherapy, as well as the increasing application of known therapies such as noninvasive ventilation, have important implications when counseling patients and families. These evolving norms provide opportunities for health professionals to consider categories of illness while simultaneously embracing uncertainty about outcomes for their patients in using a palliative care framework.

To implement appropriate palliative care, families often need an array of different providers, including doctors, nurses, social workers, psychosocial health professionals, developmental specialists, and spiritual supports. They often rely on a hospice or community-based palliative care program, a home nursing agency, or their primary care physician to help coordinate care. The care of children with serious illness may additionally involve representatives from school, camp, child life services, massage, hippotherapy, developmental therapists (eg, art, occupational, speech, physical), and others. Strong communication and reliable continuity within the team are essential. Ultimately, the goal of primary and secondary palliative care, as well as hospice care, is to promote the sense that a child's life was lived with identity and value, in contrast to a life determined by the course of illness alone.

Communicating Prognosis, Disclosure, and Decision Making

The care of children with serious illness can be marked by periods of intense uncertainty and fearful realities. Helping families determine the goals of care, appropriate treatment choices, and all aspects of planning for the child's life is facilitated by thoughtful communication. Research has found, however, that many parents feel they receive confusing, inadequate, or uncaring communication related to prognosis and treatment. They report often feeling left to reach decisions with an understanding of medical details that is different from that of their child's health professionals. Such decisions are especially difficult in a setting of misunderstanding, disagreement, or, worse, lack of trust. When feeling misunderstood or judged, parents may feel conflicted about stating their true perspective.

To this end, parents benefit from honest, clear communication about their child's illness. This is a difficult task, not only because imparting bad news is an uncomfortable and complex task but also because providing an exact prognosis is fraught with challenges. The most recent systematic reviews on prognosis prediction have found that physicians are accurate only approximately 25% of the time and tend to be overly optimistic. Although more experienced health professionals tend to err less, the longer the length of a relationship with a patient, the greater the likelihood that the prognosis they share will be incorrect. Parents nonetheless seek a clear disclosure that allows them to have a sense of the future. They interpret hidden or minimal information as evidence that the health professional is withholding frightening information. In fact, parents who receive more elements of prognostic disclosure are more likely to report communication-related hope, even when the likelihood of cure for their child is low. Often the specific details about prognosis are not necessary and instead, generalities about the expected timeline (eg, hours to days, days to weeks, weeks to months, months to years) provide sufficient information for the family's planning, coordination, and memory making. Research has also shown that earlier recognition of a poor prognosis predicts an earlier do-not-resuscitate order, decreased use of disease-directed therapies in the last months of life, and an increased likelihood of incorporating the child's comfort as a goal. It allows for some sense of control and expression of values in overwhelming circumstances.

These difficult conversations can be facilitated through a shared understanding about how a child's health and function have changed over time. When given time to reflect, families can often recognize these changes. Providing anticipatory care about feeding, breathing, or mobility changes related to the progression of illness can provide a more concrete, tangible basis for action in families related to their child's increased fragility. Uncomfortable as it is, anticipating death and addressing it clearly and frankly allows some children and families to make choices about how to spend the time remaining.

Recent research shows that health professionals can help parents feel like "good parents" to their seriously ill children by letting families know that all that can be done for their child is being done and not giving families the sense that health professionals are "quitting"; respecting parental decisions; providing comfort to the child and family; demonstrating knowledge of the particular needs of the individual child/family and that the child is uniquely special; coordinating care and providing honest, factual information; inquiring about spiritual needs; and telling parents that they are seen as acting as good parents to their child. Table 22.1 outlines a stepwise approach to communicating with children and families after prognostic information has been shared to introduce palliative concepts and better understand how to support an individual child and family in these difficult circumstances. Health professionals who support families in these ways have profound effects on meaning making and bereavement after a child's death. Even when health professionals are unsure what to say, acknowledging parents as "good parents" can show humility, build trusting relationships, and provide meaning during an incredibly difficult time.

Suffering and the Power of Hope

Initially, the topics of suffering and hope can seem to be untechnical and unprofessional to the practice of medicine. However, it is hard to imagine concepts more central to the art of healing and medicine's true purpose. Serious illness and its treatment can cause physical distress, and research has shown that dying children have many physical symptoms, such as pain, fatigue, and dyspnea (see Chapter 14). The effects of a serious illness are much larger and more complex than a physical sensation, however. Suffering was best described by Eric J. Cassel, MD, as "the state of severe distress associated with events that threaten the intactness of a person." This distress comes from a threat to any of the multiple aspects of personhood—"the lived past, the family's lived past, culture and society, roles, the instrumental dimension, associations and relationships, the body, the unconscious mind, the political being, the secret life, the perceived future, and the transcendent dimension." Some authorities recommend using terms other than "suffering" to avoid describing persons as victims or with other emotional terms that are suggestive of helplessness. Figure 22.2 shows a sample of the myriad concerning symptoms that can be interrelated for a child with serious illness, all of which must be considered when thinking about distress in seriously ill children. In caring for patients with serious illness, understanding all aspects of suffering is critical to effective care, and listening and reflection are prerequisites to the necessary healing presence required to care for dying children and their families. Pain and symptom management are foundational, but the relief of suffering requires helping a child and family struggle with issues of meaning and transcendence.

Hope evolves from expectations for or belief in a worthy future. It carries a sense of trust and resilience. Serious illness can make it difficult to know what to hope for, trust in, or rely on. Research increasingly shows, however, that aspects of hope and resiliency are sustained throughout the disappointments and upheaval associated with serious illness and even death. This process of evolving goals

Table 22.1. Communicating With Children and Families About Palliative Care

Steps and Goals	*Sample Statements*
Step 1: *Open* **Goal:** Setting a respectful tone of shared decision-making and asking permission	I would like to talk about what is ahead with your child's health and do some thinking and planning in advance. Talking about it now allows us to think things through without the pressures that come when your child is acutely ill and immediate decisions are needed. Would that be alright with you?
Step 2: *Assess* **Goal:** Understanding the family's prognostic awareness, hopes, fears, and worries	What is your understanding of where your child is now with this illness? If your child's health situation worsens, what are your most important goals for your child and your family? What are your biggest fears and worries about the future with this illness?
Step 3: *Align* **Goal:** Sharing emotional understanding of worries and wishes with the family	I see these same issues, and I am also worried that your child's health is getting worse. I wish that things were different.
Step 4: *Disclose* **Goal:** Understanding how information is shared within and with the family	How much have you and your child talked about, that is, how aware is your child of, these issues? How much information do you want, and how much information can your child handle about what is likely ahead with this illness?
Step 5: *Explore* **Goal:** Getting to a shared understanding of trade-offs and limits of interventions as perceived by the family	If your child becomes sicker, how much do you think it makes sense to have the child undergo different treatments for the possibility of gaining more time? Are there specific conditions or states that you would not find acceptable for your child to be in?
Step 6: *Close in alliance* **Goal:** Providing a summary, sharing recommendations for next steps, and expressing non-abandonment	It sounds like _____is very important to you. Given what is important to you and what we know about your child's illness at this stage, I recommend _____. Let's meet again tomorrow to talk some more. I want to make sure I am answering all your questions as best as I can.

Adapted from Goldstein RD. *Eliciting and communicating goals of care for seriously ill patients.* EQIPP Course under development, American Academy of Pediatrics, 2018.

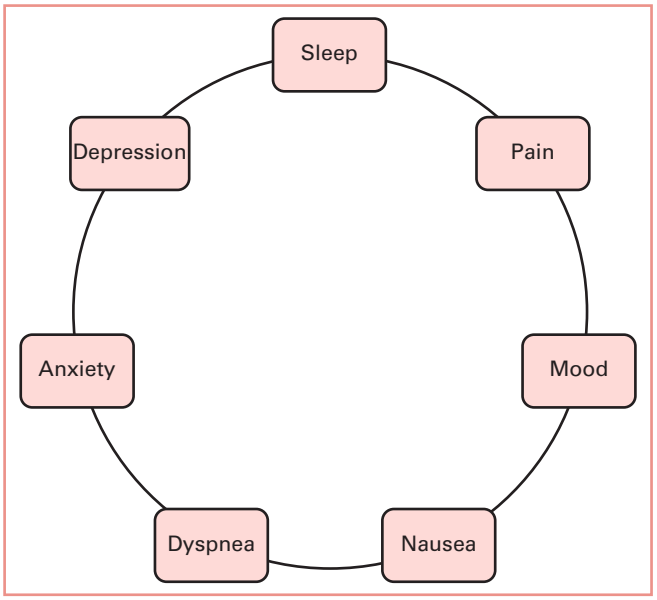

Figure 22.2. Interrelated symptoms of distress in children with serious illness.

of care or changing hopes (eg, from hope for cure to hope for time with family or a trip to the beach) occurs naturally, and families often need clear communication about what to expect to engage in this process of "regoaling." In this way, hope can be sustained when a meaningful way forward is elucidated even in the face of a dismal diagnosis or the loss of a child.

Barriers to Palliative Care

Parenting a child with serious illness can be frightening, confusing, frustrating, and exhausting. A decision to involve palliative care professionals is in no sense a decision by parents or other health professionals to stop working tirelessly for the child. It is crucial to introduce palliative care with sensitivity and thoughtfulness. Often palliative care is inaccurately viewed as an act of abandonment or "giving up." Research shows that often health professionals are reluctant to engage palliative supports for families because of perceptions of the family "not being ready" to acknowledge or accept a child's poor prognosis. This is counter to the growing body of research demonstrating that parents generally accept palliative care and believe that it is offered late. This delayed involvement of palliative care specialists results in not only worse symptom management and quality of life for ill patients, but may also result in shorter survival. Additionally, children who receive palliative care supports take fewer medications, undergo fewer invasive interventions, and are less likely to die in an intensive care unit compared with those who do not receive such care.

One of the greatest obstacles to palliative care and hospice for children has historically been lack of trained specialists. This is becoming less of a barrier as more hospitals and communities have access to pediatric palliative care specialists and with broader education, advocacy, and knowledge about the field. Workforce shortages are also eased by training in primary palliative care skills for primary care pediatricians. Despite concerns about the time needed to address a family's palliative care concerns, these practices can help pediatricians feel more useful and create deeply meaningful experiences with their seriously ill patients and families.

Another barrier has resulted from the payment model for pediatric palliative care, which historically has been based on Medicare hospice benefits that require patients to have a prognosis of 6 months or less and to forego curative care. Understandably, parents find it quite hard to give up curative efforts for their children. Although some states offer palliative care programs to remedy this, the Patient Protection and Affordable Care Act of 2010 removed the prohibition against curative treatment as a hospice benefit by or on behalf of a Medicaid or Children's Health Insurance Program eligible child. Despite these changes, eligibility still requires a physician to certify the child as likely to die in the next 6 months. It is not uncommon for children to live beyond their expected prognosis, and in these instances children can be re-enrolled to continue receiving hospice benefits. States are still not required to provide pediatric specific hospice services, however, although doing so is increasingly the norm. Advocacy for increased access to palliative and hospice services for all children with serious illness is crucial to expanding expert palliative supports for these children and their families.

A Child's Understanding of Death

Although death itself is an unknown experience, parents want to know what their children can understand during the dying process. Caregivers, too, wonder what a child knows as they try to anticipate needs or reckon with enigmatic statements from them. Most would agree that a child's distress resulting from avoidance of discussions of their fears about their condition and death is especially tragic and counterproductive.

Health professionals should, when possible, communicate with children about what is happening to their bodies, while respecting the cultural and personal preferences of each family. A developmental understanding of children's concepts of illness and death can help frame these discussions and serve to advise parents in their own conversations with their children. The understanding of a child's concept of death can be extrapolated from Piaget's work in cognitive development and is based on 4 stages: sensorimotor, preoperational, concrete operations, and formal operations. These developmental stages of understanding of death along with their typical chronologic ages, along with sample language to use when talking to children about illness and death, are shown in Table 22.2. Having limited cognitive abilities will affect a child's understanding of these issues. In contrast, illness profoundly changes development, and it is not uncommon for seriously ill children to possess a precocious and advanced understanding of certain things, such as the details of their illness or the way to address their symptoms, while simultaneously being less mature in other developmental areas.

Parents can struggle with whether they should talk with their child about the child's imminent death. Although research supports a bias toward speaking frankly to dying children, each individual situation should be considered unique and based on the child's age, cognitive development, disease, timeline of disease, parental psychological

Table 22.2. Ages and Developmental Understanding of Death

Age Group	*Conceptualization*	*Interventions*	*Example of Age-Appropriate Language*
0–2 years	No cognitive understanding of death Concern for experience of death as abandonment and/or separation Understand events in terms of direct experience Identify when adults are in distress	Maintain routines Avoid separation from significant others Presence is more important than words	"Mommy did not want to leave"
2–6 years	Believe death is temporary and reversible Often blame themselves for the death Magical thinking	Use concrete, clear, and simple language Avoid euphemisms; use "death," "dying," and "died" when possible Clarify question the child is asking Use repetition and consistent language Reflect on past experiences with the death and dying process; pet, grandparent, others Play-based activities to assist in expressing feelings	"Bobby is dead; that means he won't ever live with us again, but we will always remember him."
6–8 years	Death is final and irreversible Fear death Concerned for others' safety Believe death is not universal	Clear, realistic information Ongoing discussions about death Discuss physical details of death Establish safe space at school where the child can seek guidance when necessary	"When someone dies, that means their body is no longer working. Their heart stops beating, they no longer need to eat or sleep, their brain stops thinking, and they no longer feel any pain. They don't need their body any longer. That means we will never see them again as we could before."
8–12 years	Understand death is final, irreversible, and universal Comprehend biological aspects of death Curiosity about death and dying Intellectualize death	Open and honest discussion about one's own emotions Assure children that they will be informed about major events of concern Allow children the choice to participate in activities surrounding the death, including funeral services and hospital visits	"I, too, am very sad that Katie is sick. Grandma is going to come take care of you while I go to the hospital with Katie, but we will have Grandma bring you to the hospital if something happens."
12–18 years	Adult understanding that death is inevitable Ability to think abstractly and philosophically Curiosity surrounding existential implications of death	Support independence and access to peers Monitor social media Maintain familiar routines	"If you want to talk, I am here to listen. If you do not want to, then I am here if or when you do. I can't imagine what you are feeling right now, and I want you know I am here to support you."

Adapted with permission from Himelstein BP, Hilden JM, Boldt AM, Weissman D. Pediatric palliative care. *N Engl J Med.* 2004;350(17):1752–1762.

state, and family culture. In studies of parental disclosure to children with impending cancer death, parents who talked with their child about their death had no regrets, but among those who did not speak frankly about imminent death, more than 25% regretted not having done so. During these difficult times, primary care pediatricians can provide essential contributions to the care of seriously ill children and their families by serving as a resource for these conversations and providing guidance to families. Collaboration with pediatric palliative care specialists can support pediatricians' involvement through education and an added layer of support.

Pediatric Primary Care at the End of Life: Normal and Extraordinary

Primary care pediatricians can play an important role in the care of children with serious illness. The presence of a constant, continuous physician who understands the child, siblings, and family holistically in the community can contribute profoundly to care as part of the medical home. Because caring for these children is a rare experience in general practice, the complexities of care can be daunting. Primary care pediatricians can benefit from creating a network with others

involved in the care of the child (eg, home nurses, social workers, teachers, pediatric subspecialists, hospice) to support their direct care of seriously ill children and families throughout illness and end of life.

For seriously ill children and their families, general pediatric care from their primary care pediatrician also can be an important affirmation of the normal and can contribute to quality of life. For the child, routine health care visits, vaccinations, and developmental assessments are important, because the rationale for this care is not their disease but the positive and ordinary characteristics of childhood. The focus on development, education and learning, social engagement, play, and involvement with family and community affirms the whole child and the importance of the child's life. The primary care pediatrician is often seen as a trusted advisor who understands the family and child in this normal context and thus "knows" them best. The pediatrician is the child's doctor without qualification.

A trusted primary care pediatrician also has a role in complex disease management. The primary care pediatrician is in the best position to assess the family's level of understanding and address any gaps in that understanding. Importantly, the pediatrician can help families understand complex medical information, terminology (ie, medical jargon), and other specific medical details. They can also help the medical team better understand the patient and family perspective. The primary care pediatrician can ease the adjustment between home and hospital and help ensure more seamless transitions in either direction. Relevant involvement of the pediatrician in crucial developments requires timely sharing of information among all members of the team, the generalist, and the specialist. Ideally, the primary care pediatrician should participate in hospital-based family and provider team meetings. This is especially important during meetings in which goals of care and medical decision making are the focus. Fostering collaboration between the primary care pediatrician and the palliative care specialist is essential. Currently, this can more readily be accomplished through advances in technology, such as telehealth and videoconferencing.

When a child is facing the end of life at home, the primary care pediatrician has additional responsibilities to facilitate care for the child, siblings, and family. The primary care pediatrician can work with the hospice team to continuously fine-tune approaches to pain and symptoms. Primary care pediatricians can also play a central role in delineating resuscitation orders. Research indicates that parents consider end-of-life decisions to be the most difficult treatment decisions they face. Thoughtful conversations with a trusted primary care pediatrician who has a broad perspective on the medical details as well as the family identity and priorities is invaluable. A powerful resource to guide these discussions is the document *My Wishes*, which offers open-ended prompts with spaces to draw pictures for young school-age children to better understand their worries and hopes. *Voicing My Choices* is another excellent resource for adolescents and young adults; this resource captures not only who the patient is as a person but also the patient's end-of-life wishes. *Five Wishes* can be used when working with adults and is a legally recognized advance care planning tool when completed correctly. Another important form to consider completing with families is the Physician Orders for Life-Sustaining Treatment (POLST) form. The POLST form differs slightly by US state and serves as a home-based do-not-resuscitate order. For instance, emergency medical technicians in the field must resuscitate a child found in cardiac or respiratory failure unless orders exist to refrain. After a family has come to the difficult decision to limit interventions, it is important to advocate for these wishes in all settings and to complete documents to communicate these decisions. Asking parents to sign these forms can be heartbreaking, but framing their completion as a part of documenting a conversation can be helpful. Reaching out to local palliative care specialists to talk through the documents and communication strategies beforehand is equally beneficial.

Loss and After

The loss of a child or sibling changes life forever. It begins a process of *bereavement*, the psychological and spiritual accommodation to death on the part of the child's family, and *grief*, the emotional response caused by the loss. Grief can cause distress and physical and emotional pain, but, except in cases of prolongation, it is a normal adaptive human response, not a disease. *Anticipatory grief* begins with the awareness of impending loss or death in parents and children with sufficient awareness and cognitive development. Palliative care attends to the grief reaction before and after death. Assessing the coping resources and vulnerabilities of the affected family system before death occurs is central to the palliative care approach.

Generally, parental grief is more intense and sustained than other types of grief. Parents may never completely accept the loss of their child. Research suggests that parents who share their problems with others during their child's illness, who have had access to psychological support during the last month of their child's life, and who have had closure sessions with the attending staff are more likely to resolve their grief. Surviving siblings also grieve. The American Academy of Pediatrics recommends that primary care pediatricians reach out to children and families at the time of loss to evaluate their bereavement and to understand the personal meaning of their loss and their process of mourning. Those involved in the care of children and families appreciate how meaningful simple things, such as condolence letters and attendance at funerals or memorial services, are to families. Notes remembering the anniversary of the deceased child's birthday or helping the family think about developing the child's legacy or a remembrance also contribute to improved bereavement and meaning making after a child's death. Helping bereaved children safely remember their deceased siblings and appreciating their successes as they integrate the loss can be a powerful part of a health care visit and the long-standing caring relationship between primary care pediatricians and families. Often primary care pediatricians can be in contact with the school and other community organizations that can support bereaved siblings. When necessary, referrals to skilled mental health professionals should be offered, including referrals to bereavement specialists.

Many resources are available to support primary care pediatricians caring for seriously ill children and their families. Helpful resources include the Palliative Care: Conversations Matter campaign

(www.ninr.nih.gov/newsandinformation/conversationsmatter/about-conversations-matter) and Together for Short Lives (www.together-forshortlives.org.uk/about-us/). For families, the Courageous Parents Network (https://courageousparentsnetwork.org/) is an excellent resource that describes many aspects of caring for a seriously ill child. Most importantly, pediatric palliative care specialists locally and nationally are available to support the essential work of primary care pediatricians in their care of seriously ill patients and families. Working together, the pediatrician and palliative care specialists can address the needs of these children and their families.

CASE RESOLUTION

The hospital-based palliative care team arranged to meet with Jason's parents. During their conversation, they helped the parents articulate what gave Jason's life meaning, what happiness was for him, and what their hopes were. Jason's parents decided they would still opt for ventilatory assistance should he become compromised by an acute, likely reversible illness but could not imagine cardiac resuscitation being consistent with their goals. Therefore, a limitation was placed on cardiac resuscitation, and a POLST form was completed. With the parents' permission, the palliative care team spoke with Jason's primary care pediatrician and home nursing team.

The palliative care team continues to meet with Jason and his family for each hospital admission and connects regularly with Jason's primary care pediatrician for ongoing care transitions and health care needs.

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PART 3

Health Maintenance and Anticipatory Guidance

(*continued*)

CHAPTER 23

Neonatal Examination and Nursery Visit

Niloufar Tehrani, MD

CASE STUDY

You are performing an examination on a 16-hour-old newborn who was born at 39 weeks' gestation to a 28-year-old, healthy, primigravida via normal spontaneous vaginal delivery. No complications occurred at delivery, and the Apgar score was 8 at 1 minute and 9 at 5 minutes. The newborn weighed 3,200 g (7 lb 1 oz) and was 50 cm (19.7 in) long at birth, with a head circumference of 34 cm (13.4 in). The mother received prenatal care beginning at 10 weeks of gestation; had no prenatal problems, including infections; and used no drugs, alcohol, or tobacco during the pregnancy. Her blood type is O Rh-positive. She is negative for hepatitis B surface antigen and group B streptococcus, and she is nonreactive for HIV, syphilis, chlamydia, and gonorrhea. The father is also healthy.

On physical examination, the newborn is appropriate size for gestational age, with length and head circumference in the 50th percentile. Aside from small bilateral subconjunctival hemorrhages, the rest of the physical examination is entirely normal.

Questions

1. What aspects of the maternal and birth history are important to review before performing the neonatal physical examination?
2. What other history is important for a complete newborn assessment?
3. What aspects of the physical examination of newborns are essential to explain to parents?
4. What physical findings mandate a more extensive workup prior to discharge?
5. What is the routine hospital course for a normal newborn?
6. What are important points to cover with parents at the time of discharge for a healthy, full term newborn?
7. What laboratory studies, if any, should be performed prior to discharge?

The initial newborn physical examination is an important first encounter with the pediatrician, the newborn, and the newborn's parents all establishing relationships with each other. The key purpose of this examination is to assess the status of the newborn and detect any underlying medical problems. Relaying this information to the parent or parents is essential and answers the question foremost in a parent's mind: "Is my baby 'normal'?" By performing a physical examination in the parent's or parents' presence during the first 24 hours after the newborn's birth, pediatricians can play a major role in allaying parental anxiety. The pediatrician's role includes identifying medical problems or high-risk conditions in the prenatal screening (including ultrasonography), neonatal examination, and history. Evaluation and treatment, if necessary, can be initiated before discharge from the nursery.

Pediatric Prenatal Visit

The prenatal visit during the third trimester is recommended for all expectant families. This is the ideal time to establish the medical home and provides the pediatrician with the opportunity to speak with the parent or parents at a prenatal visit before meeting them in the hospital. The prenatal meeting provides a chance for parents to interview the physician, as well as the rest of the office staff, about general policies and procedures for well-child appointments, sick visits, and contacting the physician after hours. It also is a time to discuss what will take place at the hospital and explain the role of allied health professionals (eg, lactation specialists) in the overall care of the mother and newborn. For pediatricians and other health professionals, the prenatal visit is a time to gather vital medical information about the current pregnancy, identifying any high-risk conditions, and to inquire about any problems with previous deliveries. The pediatrician should also review any pertinent family history. In addition, the pediatrician needs to note specific needs of the parent or parents, which may include alternative medicines, cultural rituals, or ceremonies surrounding the birth of a newborn, such as circumcision. Whether the newborn will be born at home, in a birthing center, or in a typcial hospital setting, arrangements should be made to accommodate the wishes of the family.

The prenatal visit also allows physicians to assess any psychosocial issues that may negatively influence initial mother-newborn bonding, such as maternal drug use, no partner involvement, absence of a supportive social network, or lack of housing. Any of these issues may necessitate intervention by social services. The social environment that will surround the newborn at home will have a great effect on the child's future. In addition, this visit provides an opportunity to emphasize the importance of breastfeeding and educate parents on its many benefits. Anticipatory guidance issues also can be discussed, including positioning the newborn on the back to sleep, safe bedding, and child passenger safety.

Neonatal Nursery Visit

At birth, the newborn undergoes a screening examination and risk assessment by the nursery personnel when the newborn is stable after any needed resuscitation. In the absence of abnormalities, the pediatrician is notified of the birth. The American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists recommend that the pediatrician should evaluate the newborn within 24 hours after birth to identify medical conditions that need to be addressed and determine the course of newborn care. In the delivery room, the newborn is dried, Apgar scores are assigned, and the newborn is placed skin to skin on the mother's chest, with a blanket placed over the mother and newborn, to facilitate bonding and early breastfeeding.

If perinatal or delivery complications occur, such as maternal fever, maternal medication during labor and delivery, meconium aspiration, asphyxia, preterm birth, obvious newborn malformations, or distress, the newborn should be supported as necessary and kept on a radiant warmer for further assessment. The physician should be promptly notified to perform the neonatal physical examination, evaluating any problem and initiating treatment.

Evaluation

Perinatal History

The perinatal history is the beginning of the newborn's medical history and is significant in the newborn evaluation. To obtain all the pertinent history, it may be necessary to review the maternal medical record. Results of maternal laboratory tests, such as blood type; rapid plasma reagin status; purified protein derivative; HIV and hepatitis B status; chlamydial, gonococcal, and group B streptococcus cultures; and toxicology screen results should be noted (Box 23.1). The pediatrician also should obtain triple screen, prenatal ultrasonography, and amniocentesis results, if available. Maternal history, including medical conditions and medications used during pregnancy or delivery, prior deliveries, type of delivery, delivery room events, and Apgar scores should be reviewed before performing the neonatal physical examination. Given the Zika virus outbreak in the Americas in 2015 to 2016, it may be necessary to elicit travel history and perform appropriate screening in the mother and possibly the newborn. Obtaining this information helps focus the examination on findings suggested by previous medical history. Additionally, the occurrence of any unusual circumstances surrounding the delivery should be explained to the parent or parents at the time of the examination. For example, the need for a vacuum-assisted or emergent cesarean section may not have been understood. It is important to be prepared to discuss the medical implications of such events. Unexpected events related to the delivery, such as an emergency cesarean section, may be viewed as traumatic by the mother and predispose her to perinatal mood and anxiety disorders.

Box 23.1. What to Ask

Neonatal Examination

- Did the mother receive prenatal care? If so, since what month of gestation?
- Were all prenatal studies normal?
- Does either parent have a history of sexually transmitted infections, such as syphilis, gonorrhea, or herpes?
- Does either parent have a history of alcohol, tobacco, or illicit drug use?
- Did the mother take any prescribed or over-the-counter medications routinely during pregnancy?
- Did the mother have any complications, such as bleeding or decreased fetal movement, during pregnancy?
- Were there any indications of a complicated delivery, including administration of maternal medications?
- Is there a family history of congenital anomalies or diseases?
- Is the mother planning to breastfeed?
- Does the neonate have any siblings? If so, what are their ages?
- Is anyone available to help with the new baby or siblings?

Physical Examination

Every attempt should be made to perform the neonatal physical examination at the mother's bedside. This gives the physician the opportunity to meet with the parent or parents and answer all their initial questions immediately. In certain circumstances, such as preterm birth or in cases in which the mother is being treated for a medical complication, it may be impossible to perform an initial bedside examination. Regardless of the timing of the examination, the physician or other health professional should discuss the results with the parent or parents after the examination has been completed.

The neonatal examination is performed with the newborn completely unclothed and the newborn's body temperature maintained. The newborn is assessed for evidence of birth trauma and congenital malformations, and organ systems are assessed for normal physiology. The newborn's birth weight, length, and head circumference are plotted. The physician should bear in mind that these measurements are often made in the delivery room and may be subject to error. The diagnosis of small for gestational age (SGA; weight <10th percentile) or large for gestational age (LGA; weight >90th percentile) can predispose a newborn to several medical problems. Temperature, respiratory rate, and heart rate are reviewed via the nursery record. In a newborn with suspected cardiac or renal anomalies, blood pressure is also measured. Feeding, voiding, and stooling patterns are also available in the nursery record and should be reviewed.

The newborn evaluation includes an expanded Ballard score, which includes parameters for neuromuscular and physical maturity

to accurately estimate gestational age. A late preterm or near-term newborn (ie, 35–37 weeks of gestation) frequently does not have the physiologic maturity to feed vigorously and maintain body weight, glucose, or body temperature. These newborns are at high risk for readmission for treatment of jaundice, dehydration, and hypoglycemia. They should be closely followed.

The newborn's overall appearance is noted, particularly for the presence of any dysmorphic features. The physician should determine whether the newborn looks normal or has any abnormal facial features, such as low-set ears and widely spaced eyes (see Chapter 84).

Skin

In the newborn, a thick layer of white vernix caseosa composed of sebaceous secretions and epidermal cells is frequently seen. The presence and location of any rashes or birthmarks should be carefully described and pointed out to the parent or parents. The particular location of the lesion as well as the pathology of the epidermal lesion may aid in specific diagnosis of it. Skin lesions resulting from birth trauma are documented and managed as necessary. Bruising should be differentiated from the benign dermal melanocytosis that often occurs in the sacral area. Skin color is noted. Cyanosis may be indicative of congenital heart disease, the presence of jaundice is suggestive of hyperbilirubinemia, and plethora may be a sign of polycythemia.

Head

Head size and shape are evaluated, including the size of the fontanels and position of the sutures. The head may be significantly molded into a cone deformity secondary to pelvic pressure at the time of delivery. This deformity resolves within days after birth, which may result in a significant change in the head circumference. A *cephalohematoma*, which is a subperiosteal bleed that does not cross the suture line, appears as a unilateral or bilateral discrete lump on the side of the head. This finding may predispose the newborn to hyperbilirubinemia, and it may take up to 2 months for the condition to resolve. A cephalohematoma should be differentiated from a *caput succedaneum*, which is scalp edema that crosses the midline and may be ballotable. Edema usually resolves rapidly. Skull fractures may occur with birth trauma and may present as a step-off or crepitus on palpation of the skull. Such fractures are associated with cephalohematoma, but treatment is rarely required. Any unusual findings about the head may be a source of parental concern.

Eyes

The eyes are evaluated for subconjunctival hemorrhages, colobomas, pupillary reaction, extraocular movements, and presence of red reflexes. If it is not possible to elicit a red reflex, an ophthalmologic evaluation is essential. Absence of this reflex is suggestive of conditions such as congenital cataracts or retinoblastomas. The color of the sclera and the spacing and symmetry of the eyes are also evaluated, because abnormalities may be suggestive of an underlying syndrome. For example, upslanting palpebral fissures can be seen in the setting of trisomy 21, and blue sclerae may be indicative of osteogenesis imperfecta.

Ears

The placement, size, and shape of the ear pinnae are noted as well, along with any preauricular or postauricular pits or appendages. The presence of a significant auricular abnormality may correlate with hearing loss or be suggestive of a genetic syndrome and necessitates further evaluation.

Nose

The nose is checked carefully for patency of the nares. This is easily accomplished by occluding airflow from 1 nostril and observing airflow from the other. Choanal atresia is an important condition to rule out, because newborns are obligate nose breathers until 3 months of age, and choanal atresia may result in respiratory distress. A nasal fracture also can occur during the delivery process. Such fracture presents as an asymmetric nose. If the physician presses on the nasal tip and the nares are symmetric, the diagnosis is a deformity that will resolve. If the nose falls to 1 side, however, the presence of a nasal septum fracture is probable, and prompt evaluation by an otolaryngologist is warranted.

Mouth

The oropharynx is examined closely for any defects in the hard or soft palate. A bifid uvula may be indicative of a submucosal defect of the soft palate that may be difficult to appreciate without palpation (see Chapter 85). Common normal findings in the oropharynx, including Epstein pearls located at the midline on the hard palate and epithelial cysts along the gum line (ie, Bohn nodules), are also noted. Loose natal teeth should be removed to prevent the possibility of aspiration (see Chapter 31). The tongue is evaluated for macroglossia or a tight lingual frenulum (ie, ankyloglossia), which may interfere with effective breastfeeding.

Neck

The neck is palpated for sternocleidomastoid hematomas, masses, torticollis, and skin redundancy. The clavicles are evaluated for fractures, which are more common in newborns who are LGA or in the setting of a delivery complicated by shoulder dystocia.

Chest

The chest is inspected for respiratory effort and the lungs auscultated to ensure normal breath sounds throughout. The quality of the newborn's cry is assessed as well. Laryngeal webs or a paralyzed vocal cord may present in the newborn. Chest wall deformities, such as pectus excavatum, are noted. If an absent rib is suspected, a chest radiograph should be obtained. The presence of breast buds is normal; however, supernumerary nipples are minor malformations, although no treatment is indicated. Widely spaced nipples are a common minor malformation in patients with Turner syndrome.

Heart

The heart is auscultated to ensure that it is in the proper position on the left side of the chest. Femoral and brachial pulses are palpated. The physician should listen for and document the presence of cardiac murmur. The presence of a murmur does not always

indicate complex congenital heart disease. In the first 24 hours, a murmur may be a closing ductus; additionally, newborns can have functional murmurs. *Peripheral pulmonic stenosis* is a common benign heart murmur in the newborn that is characterized by transmission to the right side and back. The AAP, American Heart Association, and American College of Cardiology recommend universal screening for critical congenital heart disease by pulse oximetry reading for which the AAP algorithm is most commonly used (Figure 23.1). However, every murmur should be evaluated on an individual basis. If further assessment is indicated, 4 extremity blood pressures, an electrocardiogram, and a chest radiograph should be obtained. The presence of abnormal findings or a murmur associated with cyanosis, tachypnea, poor feeding, or congenital anomalies is highly suspicious for a pathologic cause. A consultation with specialists in pediatric cardiology should be sought and an echocardiogram obtained.

Abdomen

It is easiest to palpate the abdomen before feeds. The abdomen is assessed for any masses or organomegaly (eg, polycystic kidneys, hepatosplenomegaly, adrenal hemorrhage) that warrant further investigation. Bimanual palpation may be helpful to identify masses. The umbilicus is examined to identify 3 vessels as well as the quality of the cord. A small, atretic cord can be the cause of low weight in the newborn. Erythema and swelling of the skin around the cord may be indicative of omphalitis, which is a serious infection.

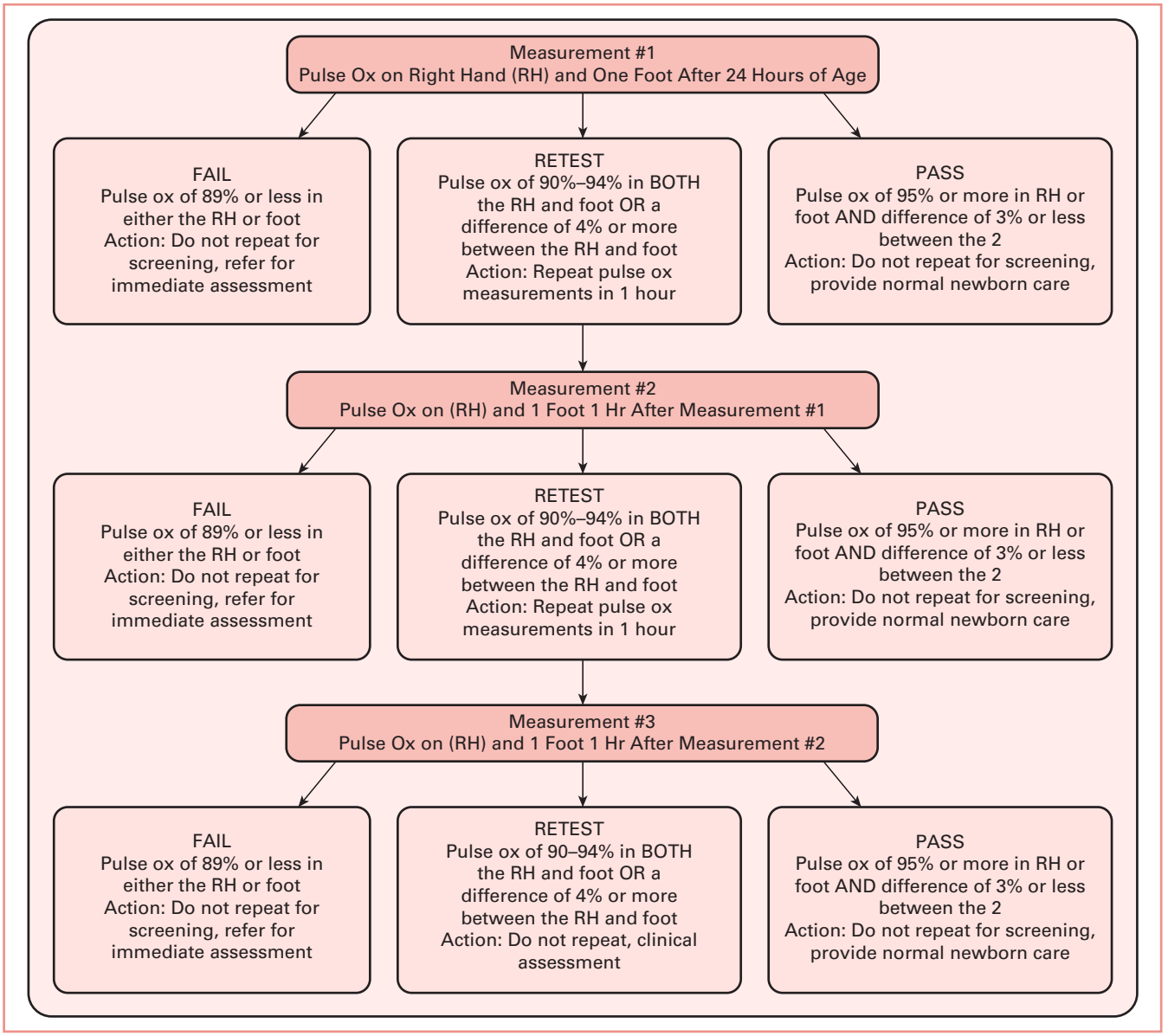

Figure 23.1. Critical congenital health disease screening protocol.

Abbreviation: pulse ox, pulse oximetry.

Reprinted with permission from Ewer AK, Martin GR. Newborn pulse oximetry screening: which algorithm is best? *Pediatrics.* 2016;138(5): e20161206.

Genitalia

In female neonates, the labia majora may be swollen, but the urethra and vaginal opening should be visualized to ensure patency. Hymenal tags are a common finding. Clitoral size is noted. Parents should be told that a physiologic vaginal discharge and the presence later of a pink or blood-tinged discharge are a normal neonatal response to maternal estrogen withdrawal. In male newborns, the penis is examined for size and length. The foreskin should be retracted sufficiently to reveal the location of the urethral meatus to assess for hypospadias. A testicular examination can rule out hydroceles, inguinal hernias, and cryptorchidism. Atypical genitalia may be indicative of an underlying disorder, such as congenital adrenal hyperplasia or disorders of sexual differentiation, and necessitates further evaluation (see Chapter 107).

Anus

The patency and location of the anus are assessed. Patency is confirmed after the newborn passes meconium, typically by 48 hours of age. An imperforate anus may be an isolated finding, or it may be indicative of a syndrome, such as vertebral, anal, cardiac, tracheal, esophageal, renal, and limb syndrome.

Skeleton

The newborn skeleton is assessed for evidence of skeletal dysplasia. All long bones are examined for a potential fracture secondary to birth trauma. The neonatal hip examination is important to detect developmental dysplasia of the hip, which is most likely to occur in cases of a breech position in utero. The Ortolani maneuver is performed to detect a dislocated hip. The "clunk" felt when performing the examination is the relocation of the femoral head of the affected hip in the joint capsule. In contrast, a "click" may be indicative of normal perinatal ligament laxity. The Barlow maneuver detects an unstable hip that may be at risk for dislocation. A positive result on either test is indicative of a hip that is or could be dislocated and warrants an orthopedic consultation. Treatment with a Pavlik harness is initiated until confirmatory testing on ultrasonography is reliable at 6 weeks of age (see Chapter 113). The spine is palpated completely to the sacrum. Sacral defects, deep sacral pits, or sacral tufts of hair warrant an investigation for conditions such as spina bifida occulta. The fingers and toes are counted and assessed for syndactyly or other abnormalities. The feet may be turned inward, outward, or up and are gently moved to a normal position to ensure flexibility. Deformities secondary to intrauterine pressure are common. Clubfoot or equinovarus deformations warrant evaluation by an orthopedic surgeon.

Neurologic Examination

A newborn's resting position is assessed to evaluate tone. All extremities should be flexed. The newborn then can be held prone for further evaluation of tone. Newborns are observed for motor activity, that is, moving arms and legs symmetrically. Response to sensory stimulation and deep tendon reflexes should be elicited. Facial movements are closely observed for symmetry. Primitive reflexes, such as suck, rooting, grasp, stepping, and especially Moro, are an important part of the newborn neurologic examination. The behavior of the newborn also can yield information about an intact neurologic system. The newborn should respond to sound, fixate on a face, and be capable of attempts at self-consolation.

Normal findings of the nursery physical examination are summarized in Box 23.2. Significant findings should be addressed

Box 23.2. Common Benign Physical Findings in Newborns

Skin
- Milia
- Erythema toxicum
- Salmon patch
- Nevus flammeus
- Hemangiomas
- Dermal melanosis
- Lanugo (ie, body hair)
- Vernix

Head
- Cephalohematoma
- Caput succedaneum
- Molding

Face
- Swollen overall appearance
- Minor malformations

Eyes
- Swollen eyelids
- Subconjunctival hemorrhages

Ears
- Preauricular appendages/pits
- Folded pinnae

Nose
- Flattened nose
- Milia over bridge

Mouth and Throat
- Epstein pearls
- Epithelial pearls
- Natal teeth
- Shortened frenulum

Chest
- Supernumerary nipples
- Breast buds
- Galactorrhea
- Pectus excavatum or carinatum

Genitalia
- Females: swollen labia, hymenal tags, vaginal discharge
- Males: hydrocele, undescended testicle (palpated in inguinal canal)

Hips
- Click or clunk sound

Extremities
- Feet turned up, in, or out, but malleable

Neurologic Examination
- Primitive reflexes: Moro, grasp, rooting, stepping

immediately when noted at the initial nursery examination, including evidence of hydrocephalus, a ductal-dependent cardiac lesion, cyanotic congenital heart disease, a diaphragmatic hernia, an abdominal mass, or a possible chromosomal abnormality (eg, trisomy 13 or trisomy 18), all of which can be life-threatening. The physical conditions associated with trisomy 21 are rarely life-threatening, although suspicion of the diagnosis warrants consultation with a geneticist as well as evaluation for cardiac, abdominal, and other anomalies (see Chapter 42).

Laboratory Tests

Few laboratory tests are necessary for the healthy newborn. The only test that all newborns in the United States receive is the state-mandated newborn screening test prior to discharge from the nursery (see Chapter 25). Heel-stick blood usually is evaluated for inherited conditions, such as phenylketonuria, galactosemia, hypothyroidism, hemoglobinopathies, cystic fibrosis, congenital adrenal hyperplasia, and inborn errors of metabolism. The newborn screen varies by state and depends on the prevalence of a particular disease in a given region (see Chapter 25). In all states, hearing screening is also part of the mandated newborn screening. Screening methods may be by automated auditory brainstem response, otoacoustic emission testing, or conventional auditory brainstem response. The newest screening test is the addition of pulse oximetry at 24 hours of age to rule out transposition of the great vessels, tetralogy of Fallot, hypoplasia of the left heart, and other critical congenital heart disease.

Serum glucose testing may be performed for newborns at high risk for hypoglycemia, such as newborns who are SGA or LGA, newborns of diabetic mothers, and symptomatic newborns. Evaluation of hematocrit level is necessary in jaundiced, pale, or ruddy-appearing newborns; SGA and LGA newborns; and twins and multiples. In cases of ABO or Rh incompatibility, it is important to perform serum bilirubin and antiglobulin (ie, Coombs) tests. Screening for hyperbilirubinemia to prevent kernicterus is recommended for all newborns. Bilirubin screening is easily done by a transcutaneous reading; if the transcutaneous reading is elevated, the serum level is evaluated as well (see Chapter 126).

Imaging Studies

Routine radiographs are not indicated in neonates whose examination is normal and should be ordered only if indicated by the examination. Some minor malformations, such as pectus excavatum, do not require radiographic evaluation. Vertebral radiography, ultrasonography of the lumbosacral spine, or magnetic resonance imaging are appropriate in the neonate with a deep sacral pit or sacral tuft of hair in patients in whom spina bifida occulta is suspected. Clavicular radiographs are indicated in the patient with swelling or pain located in the clavicular area or in whom an asymmetric Moro reflex is elicited. A chest radiograph, electrocardiogram, and echocardiogram are warranted for a significant murmur. If hydronephrosis was detected on prenatal ultrasonography, follow-up renal ultrasonography should be performed in the neonatal period. If multiple anomalies are found, renal ultrasonography should be performed to evaluate for malformations of the kidneys; a skeletal survey may be helpful as well. More extensive studies are indicated in cases in which an emergent physical finding is discovered.

Management

After stabilization in the delivery room, the newborn is thoroughly dried and given to the mother for breastfeeding and bonding. If mother and baby are healthy, the newborn should stay with the mother. Every hospital should encourage rooming-in of the newborn with the mother. The newborn should feed in the delivery room if breastfeeding or within 2 hours of birth if formula feeding and continue to feed every 2 to 3 hours to prevent hypoglycemia. The preferred feeding method is breastfeeding, and the mother should receive sufficient postpartum support to ensure success (see Chapter 29). An initial bath is only necessary to remove blood or meconium after the newborn's temperature is stable. The administration of intramuscular vitamin K to prevent hemorrhagic disease of the newborn and the application of ophthalmic antibiotic ointment or silver nitrate in the newborn's eyes to prevent gonorrheal infection is universal. Hepatitis B vaccine is recommended for all newborns at birth regardless of mother's serology; based on maternal risk factors (eg, history of maternal IV drug use), hepatitis B immune globulin should also be considered.

Vital signs are monitored every 30 minutes until stable during the transition to extrauterine life (which can last 4–8 hours), then every 4 hours. Daily weights as well as strict documentation of voiding and stooling patterns are necessary to monitor the newborn for adequacy of intake and signs of potential dehydration. Weight loss is expected, but loss of more than 7% of birth weight requires physician assessment. Umbilical cord care remains controversial, but in developed countries, leaving the cord to dry is sufficient treatment.

If desired, circumcision is usually performed on the day of discharge (see Chapter 27). The newest guidelines from the AAP note that the benefits of circumcision outweigh the risks. Local anesthesia is universally recommended for the procedure. After the procedure, parents are instructed to leave the gauze or Plastibell device in place. It will fall off spontaneously. Petroleum ointment may be placed on the corona of the penis to prevent it from sticking to the diaper. The physician should be notified if excessive bleeding or oozing occurs (eg, soaking of the diaper with blood) after discharge from the nursery.

Discharge Planning and Counseling

In most cases, mother and newborn should be discharged home together. The recommended hospital stay is 48 hours for a vaginal delivery and 96 hours for a cesarean section. The physician should reexamine the newborn on the day of discharge to identify problems that may have developed and counsel the parent or parents. A bilirubin assessment is required. This examination is best performed at bedside. The newborn's physical findings and hospital course should be reviewed with the parent or parents. If studies other than routine neonatal screening were performed, the physician should also share those results.

Discharge is the best time to review anticipatory guidance issues. Topics that should be covered at the bedside include feeding patterns and what to expect, sleeping and elimination patterns in the newborn, umbilical cord care, bathing the newborn, and safety issues (eg, car safety seats, sleeping position, safe sleep environments). Guidelines on symptoms of illness and when to call the office or emergency department also should be addressed. These include a rectal temperature of 38.0°C or above (≥100.4°F), respiratory distress, irritability, lethargy, decreased feeding, and evidence of dehydration. If parents have any concerns about their newborn, they should be encouraged to call the physician's office. A follow-up visit should be arranged at 3 to 5 days of age for any newborn being breastfed to give breastfeeding support and to assess the newborn for evidence of jaundice or dehydration. An early follow-up appointment may also be indicated in a newborn with social risk factors and near-term newborns who are at increased risk for complications. If the newborn is born via cesarean section or is formula feeding, a follow-up visit at 1 week after discharge may be appropriate.

Early newborn discharge is an option if desired by the mother. The AAP has published guidance recommendations on discharge of the newborn younger than 48 hours. Generally, the history, including social risk factors, physical examination, and hospital course, all should be low risk and the newborn should have been observed for at least 12 hours. If the newborn is stable and is sent home at less than 48 hours of age, a mandatory follow-up appointment should be scheduled within 2 days of discharge. The newborn born at home should undergo medical evaluation within 24 hours of birth and again 48 hours after the first evaluation. Hospitalists have been assuming more of the hospital care for newborns in many communities. The complete hospital record and results of screening tests must accompany the newborn to the medical home. This coordination of transfer of care can be challenging, but it is essential for optimal care.

CASE RESOLUTION

The parents should be advised that the newborn's weight, length, and head circumference are all normal. The examination is reviewed at bedside, and the subconjunctival hemorrhages should be shown to the parents and their benign, self-limited nature explained. Parents should be reassured about all other normal aspects of the physical examination. The newborn's blood type from cord blood should be obtained, because the mother has blood type O Rh-positive. Routine neonatal screening, feeding, sleeping, elimination, bathing, and safety should be reviewed. Before discharge, the newborn should receive the hepatitis B vaccine and should undergo newborn screening tests and bilirubin assessment. A follow-up appointment should be made for 48 hours after discharge to follow breastfeeding progress. Results of all newborn screening tests should be reviewed when available.

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CHAPTER 24

Maternal Perinatal Mood and Anxiety Disorders: The Role of the Pediatrician

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CASE STUDY

You are evaluating a 3-week-old boy who is the product of a 39-week gestation pregnancy to a 30-year-old gravida 1, para 1 mother who has been breastfeeding the newborn. The newborn's birth weight was 3,650 g (8.0 lb), and the newborn now weighs 3,380 g (7.5 lb). The mother expresses concern about her ability to breastfeed. She also admits to being exhausted and feeling detached from the baby. She is overwhelmed by being a mom, something she had looked forward to since she was a little girl. She has difficulty concentrating and has no appetite. She asks you if it is normal to feel this way.

Questions

1. What is the spectrum of perinatal mood and anxiety disorders?
2. What are the signs and symptoms of perinatal mood and anxiety disorders?
3. What are the risks to newborns of mothers who experience perinatal mood and anxiety disorders? To older children?
4. What is the role of the pediatrician in assessing mothers for perinatal mood and anxiety disorders?
5. What screening instruments are available to assist in assessing mothers for perinatal mood and anxiety disorders?
6. What are the risks and benefits of the use of psychopharmacology during pregnancy and postpartum if breastfeeding?
7. What resources are available to offer to mothers who may be experiencing perinatal mood and anxiety disorders?

The term *perinatal mood and anxiety disorders* (PMADs) is the preferred nomenclature to denote the spectrum of mental health issues facing mothers (and fathers) related to the pregnancy and birth of a neonate. Peripartum depression had been used to encompass a cadre of mental health problems that new mothers may experience, but now there is recognition that mental health issues can be present preconception, through pregnancy, and into the infant's first postnatal year. These issues include not only depression but other mental health disorders. Despite public disclosures and open discussions by celebrities such as Brooke Shields and Gwyneth Paltrow, these conditions are under-recognized, and as a result, many mothers go undiagnosed and untreated. The stigma related to mental health is a barrier to maternal disclosure and seeking help. Too often, maternal symptoms are dismissed as fatigue related. The pediatrician is in an ideal position to assess a mother for these symptoms following the birth of a baby because the pediatrician usually sees the mother-baby dyad prior to the obstetric postpartum visit at 6 weeks following the baby's birth. The recommended time points for screening for PMADs coincide with health supervision visits: 2 weeks, 2 months, and 6 months. In addition, women are likely to follow up with their baby's pediatric appointments more than their own. While fatigue is a common report of new mothers as well as new fathers, other symptoms, particularly those of impaired functioning and diminished ability to care for the baby, may suggest a more significant disturbance.

Epidemiology

Maternal depression is the number 1 complication of pregnancy, exceeding diabetes and hypertension. The incidence of perinatal depression varies with the population studied, with the estimated range being from 5% to 25%. Between 15% and 25% of pregnant women experience depressive symptoms while pregnant, and approximately 13% of women take an antidepressant at some time during their pregnancy. Women who experience depressive symptoms during pregnancy are twice as likely to be depressed postpartum as those with no depressive symptoms while pregnant. The prevalence of PMADs is much higher at 40% to 60% in certain

groups, including women in low-income households, certain ethnic minorities (including Hispanic, black, and Native American), pregnant and parenting teenagers, mothers of multiple births, women who served in the military, and members of the lesbian, gay, bisexual, transgender, questioning/queer, intersex (LGBTQI) community. The World Health Organization notes that depression is the fourth leading cause of disease burden in the world. In spite of the high prevalence across all groups, fewer than 50% of cases of PMADs are identified.

Often, there is reluctance on the part of obstetricians or psychiatrists to treat pregnant women with antidepressants because of concerns about the potential adverse effects of the medications on the developing fetus. These potential effects include fetal malformations, cardiac defects, pulmonary hypertension, and reduced birth weight. However, untreated PMADs in pregnancy increase the risk of preterm delivery, low birth weight, and a newborn's own ability to regulate emotions and stress. The American College of Obstetricians and Gynecologists and the American Psychiatric Association have issued joint guidelines on the management of pregnant women with depression, which include indications for psychotherapy as well as psychopharmacology in the pregnant woman. Pediatricians are usually not involved in this part of the decision-making process but should be knowledgeable about the possible complications that the newborn may experience following birth from exposure to antidepressants or untreated maternal mental illness. The issue of psychotherapeutics in breastfeeding mothers is also relevant to the pediatrician. Approximately 6% to 10% of fathers experience peripartum depression, with the highest rates seen between 3 and 6 months following the birth of the baby. Paternal rates of depression are higher when there is maternal depression, and the effect on the infant is greater than if the father is not affected. Depressed fathers have an increased rate of substance use.

There is a wide range of symptomatology that can be categorized as PMADS (Box 24.1). *Baby blues* or *maternity blues* are used to describe the very common experience of new mothers, said to affect 50% to 80% of postpartum women in the first few days after delivery. There is no *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (*DSM-5)* categorization of baby blues. Generally, symptoms improve over 1 to 2 weeks and functioning is not impaired, although baby blues may herald later depression. Mothers experience sadness, crying, mood swings, anxiety, and worrying.

A diagnosis of *peripartum depression* meets the criteria of depression according to *DSM-5,* which include a depressed mood, diminished pleasure (anhedonia), changes in appetite and sleep, psychomotor agitation or retardation, fatigue, feelings of worthlessness or inappropriate guilt, decreased ability to concentrate, and recurrent thoughts of death or suicide. Suicide is the leading cause of death in mothers during the first year postpartum. Technically, symptoms of depression must begin within 4 weeks of delivery and may persist for 1 year, although the onset is often insidious and does not come to medical attention until later than 1 month postpartum.

Postpartum psychosis is less frequent, occurring in 1 to 3 per 1,000 deliveries within the first 4 weeks after delivery. There is severe impairment, with paranoia, mood shifts, hallucinations, delusions, and suicidal and homicidal ideation. Sometimes there is a history of a preexisting bipolar disorder. Affected mothers require hospitalization, in part because the infanticide rate is 4% to 5%.

Box 24.1. Perinatal Mood and Anxiety Disorders Symptomatology

Baby Blues
- Sadness
- Crying
- Mood swings
- Anxiety
- Worrying
- First few days after delivery
- Resolves in 1–2 weeks

Peripartum Depression
- Meets *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition, criteria for depression
- Depressed mood
- Diminished pleasure
- Change in appetite
- Change in sleep
- Fatigue
- Feelings of worthlessness or guilt
- Inability to concentrate
- Recurrent thoughts of death or suicide

Postpartum Psychosis
- Severe impairment
- Paranoia
- Mood shifts
- Hallucinations
- Delusions
- Suicidal/homicidal ideation
- Usually requires hospitalization

Other disorders that have been recognized as being pregnancy and birth related or exacerbated include anxiety disorders, panic disorder, postpartum posttraumatic stress disorder, postpartum bipolar disorder, and postpartum obsessive-compulsive disorder; 5% of mothers report intrusive thoughts of harming their baby.

It is estimated that 400,000 neonates are born to mothers who are depressed. These neonates are at risk for a host of adverse physical and developmental consequences.

Pathophysiology

The precise pathophysiology of PMADs has yet to be elucidated, but sleep deprivation related to the demands of caring for a newborn, genetic factors, other biological or inflammatory processes (cytokines), and hormonal changes are felt to be contributing factors. While there are rapid decreases in the levels of estrogen, progesterone, and cortisol, the hormonal levels noted in mothers

who experience peripartum depression do not differ from women who do not experience peripartum depression. Perhaps more significantly, there are a number of risk factors that have been associated with its development, including prior history of depression in general but especially during a previous pregnancy; mood disorders, including premenstrual dysphoric disorder; substance use; alcohol dependence; low socioeconomic status; a history of infertility; prior perinatal loss (eg, miscarriage, sudden unexpected infant death, bed-sharing death); lack of social support or community network; unintended or unwanted pregnancy; or a family history of depression. Other social or familial factors include marital discord, divorce, and intimate partner violence. Homicide is the leading cause of death among pregnant women. It is important to recognize that depression can affect adoptive mothers, who experience stress and anxiety during the adoptive process, remain concerned that the birth mother may reclaim her baby, have issues related to prior infertility, and tend to have less familial support.

Peripartum depression is less easy to recognize in fathers. Paternal depression is often covert or masked. Fathers are less likely to seek help or have ongoing access to health professionals. They may feel excluded from the mother-baby relationship. Often, they become workaholics as a means of coping with depression.

Evaluation

Mother

Screening for PMADs is within the scope of the pediatric practice. Studies have shown that mothers are comfortable being queried by pediatricians about how they are doing. Some pediatricians express concern about the appropriate strategies for screening and what to do if they determine that a mother has symptoms of depression.

It is important to couch any depression screening in language that makes a new mother feel comfortable and not judged in any way. Postpartum Support International promotes the "universal message" to share with depressed new mothers: You are not crazy; you are not alone; and with the right help, you will get better.

There are several instruments used to screen for PMADs. A simple tool, called the Patient Health Questionnaire-2 (PHQ-2), begins with a background statement related to depression as a common and treatable condition that often goes unrecognized. There follows justification citing the recommendation of the US Preventive Services Task Force that all adults be checked for depression. The question, "Over the past 2 weeks, how often have you been bothered by any of the following problems?" is asked, with the following 2 categories: "Little interest or pleasure in doing things," and "Feeling down, depressed, or hopeless." For both categories, the following responses are possible: 0, not at all; 1, several days; 2, more than half the days; 3, nearly every day. A score of 3 or more has a sensitivity of 83% and a specificity of 92% for major depressive episode and indicates the need for a more extensive assessment to make the diagnosis of depression.

A second instrument is the *Edinburgh Postnatal Depression Scale* (*EPDS*), which is available on the internet at no cost. A sample question from the scale is given in Box 24.2. The scale was developed in 1987 and consists of 10 questions completed by the mother. The mother is asked to check the response that comes the closest to how she has been feeling in the previous 7 days, with there being 4 choices ranging from "often" to "never." All items must be completed, and the mother must respond by herself unless she has limited English skills and the questionnaire has not been provided in the mother's native language. The maximum score is 30. A score greater than 10 indicates risk for depression. A positive response to question 10, which asks about suicidality by itself, is considered a positive screening result. The instrument is available in more than 40 languages.

Box 24.2. Sample Question From *Edinburgh Postnatal Depression Scale*

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

Here is an example, already completed.

I Have Felt Happy:

☐ Yes, all of the time.
☒ **Yes, most of the time.**
☐ No, not very often.
☐ No, not at all.

This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.

Adapted with permission from Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* 1987;150:782–786.

A third instrument is the Patient Health Questionnaire-9 (PHQ-9). Like the *EPDS*, the PHQ-9 includes 10 questions (9 questions and a follow-up question if any of the first 9 indicated any problems) related to the signs and symptoms of depression. The respondent notes whether the symptoms are present "not at all," "several days," "more than half the days," or "nearly every day." A score is then generated based on the mother's answers to assess her degree of depression. Mothers may be asked to complete these questions while in the waiting area. The PHQ-9 is not limited to postpartum mothers but can be used for all patients older than 18 years. Some electronic health records require the PHQ-9 as part of routine annual health screening.

Infants and Children

Infants and children may experience a number of problems as a consequence of maternal depression. Exposed children may develop disorders of attachment, particularly insecure attachment, and are at risk for the subsequent development of conduct or other behavior disorders. Language development may be adversely affected because depressed mothers speak fewer words and have fewer social interactions with their children. Maternal depression has also been associated with the decision not to breastfeed or the early cessation of breastfeeding. Classic environmental failure to thrive can be related to maternal depression and reduced mother-baby interactions. The effects of maternal depression can be detected in 2-month-olds who

regard mothers who have depression less frequently, have poorer state regulation, interact with objects less frequently, and have lower levels of overall activity than infants of mothers who do not have depression. These symptoms are attributed to the notions of the need for reciprocity between the mother and infant: mirror neurons, skill beget skill, and serve and return. The persistent absence of responsive care disrupts brain development. Long-term effects of maternal depression on child development have been demonstrated in magnetic resonance imaging of the brains of such children and increased cortisol levels at the time of school entry. Children are characterized as anxious, wary, and withdrawn. Social skills are noted to be poor. Early diagnosis and intervention may prevent the development of these problems.

Management

The major role of the pediatrician is to assist in the early identification of mothers who are experiencing PMADs and to make the appropriate referral for more definitive management. Support for this recommendation comes from a number of sources, including the 1999 and 2001 reports of the US Surgeon General; *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents;* the American Academy of Pediatrics (AAP) National Resource Center for Patient/Family-Centered Medical Home; and AAP policies on family-centered care. Practices that include the presence of social workers or mental health specialists can avail themselves of these individuals to assess, counsel, and refer mothers as appropriate. The mother may be referred back to her obstetrician for a visit prior to the 6-week checkup. Alternatively, mothers may be referred to local mental health specialists when such resources are known and available.

The pediatrician should also be familiar with the possible adverse effects of psychotropic medications on the fetus and newborn and recommendations about these medications in relation to breastfeeding. The decision to initiate psychotropic medication ingestion during pregnancy is made by the obstetrician or psychiatrist caring for the mother. There is no antidepressant specifically approved by the US Food and Drug Administration for use during pregnancy. All antidepressants cross the placenta and are never category A (no risk). Animal studies reveal no teratogenic effects of these medications, and the treating physician has to balance the risks of untreated depression versus the use of selected serotonin reuptake inhibitors (SSRIs). Paroxetine (eg, Paxil) has been associated with abnormalities of the right ventricular outflow tract. There is an increased risk of a septal defect with the use of any SSRI. It is noted that the risk of preterm labor increases from 6% to 22% when SSRIs are used, but the risk of preterm labor with untreated maternal depression is 20%. Newborns who have been exposed to SSRIs may exhibit poor neonatal adaption or neonatal abstinence syndrome. Symptoms include respiratory distress, irritability, jitteriness, hypotonicity, poor latching and feeding, and, rarely, seizures. The prevalence of persistent pulmonary hypertension increases from 1 to 6 in 1,000. Even if the mother is on an SSRI, she should be encouraged to breastfeed. As it relates to the use of SSRI and breastfeeding, we have the most experience with sertraline (eg, Zoloft) and paroxetine. Low levels of drug are detected in human milk but are not detected in the newborn's blood. If the mother is on a different medication, checking the medication website may provide additional information. Of note, there is a newly licensed medication, brexanolone, which appears to be effective for severe postpartum depression. To date there is no information related to breastfeeding and the use of brexanolone, but treated mothers have all been hospitalized because of the severity of their depression.

There are a number of internet sites that are very helpful in providing information about community resources. Postpartum Support International (www.postpartum.net; 800/944-4PPD [4773]) provides geographically specific information. The website can be accessed even while the mother is in the pediatrician's office. It is also important to have an emergency protocol in place, such as calling 911 or a psychiatric emergency team, should a woman endorse suicidality while in the pediatrician's office. Having such resources and protocols in place can go a long way toward reducing pediatricians' anxiety about screening for depression and suicidality.

Some perinatal programs offer home visitation or the use of doulas (ie, women who support other women through labor and delivery and after the birth of a baby in a nonmedical capacity), which assist mothers-to-be as well as recent mothers with the demands of birth and parenting. Such programs may offer a preventive and early intervention approach to peripartum depression by offering help and emotional support to new mothers as well as by screening for PMADs on a routine basis.

Older children who have been affected by maternal depression may be treated with other modalities that focus on mother and child to help address attachment disorders. Research on these dyadic interventions has demonstrated they are associated with decreased psychiatric symptoms and significant improvement in functioning of the mother and child. Internalizing and externalizing child behaviors are reduced when maternal depression, anxiety, or other conditions are addressed. Some programs include parent-child interactive therapy and parent-child psychotherapy. The program Circle of Security International involves video-based intervention that focuses on strengthening care giving.

Prognosis

The prognosis for PMADs and their effects on newborns, infants, and children are contingent on early recognition and appropriate intervention. Promoting screening is critical to ensuring a positive outcome. Pediatricians still face barriers, however, including the need to screen for a number of other conditions (eg, parental smoking, interpersonal violence), insufficient time, inadequate training, lack of appropriate resources, and lack of payment for services. A number of models have demonstrated that screening for PMADs can be successfully undertaken in a pediatric practice. The Assuring Better Child Health & Development project has been implemented in 28 states and involves the AAP chapters in those states. Pediatricians in Illinois, for example, can be paid through Medicaid if they administer the *EPDS*. *Bright Futures,* the health supervision guidelines developed by the AAP, endorses assessing parental social and emotional

well-being. Incorporating questioning into the health supervision visits at 1, 2, 4, and 6 months is recommended. Additional information about individual state initiatives can be found at the National Academy for State Health Policy ABCD Resource Center website (www.nashp.org/abcd-resources).

CASE RESOLUTION

While many of this mother's symptoms are common, her self-assessment that she is unable to function suggests that she is experiencing peripartum depression rather than baby blues. You ask her if it is all right to contact her obstetrician to see if she could be seen sooner. She agrees. When you reach her obstetrician, she schedules the mom to come in the following morning. The obstetrician tells you she has a therapist in her office who will be able to meet with the mother at that time.

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CHAPTER 25

Newborn Screening

Henry J. Lin, MD, and Moin Vera, MD, PhD

CASE STUDY

A 1-week-old boy is brought to the pediatrician's office for a positive newborn screening test result for congenital adrenal hyperplasia. The baby was a product of a 38-week gestation and was born by normal spontaneous vaginal delivery to a 30-year-old gravida 2, para 2 woman with an unremarkable pregnancy. Birth weight was 3,300 g (116.4 oz), and the baby is feeding and acting appropriately. Family history is unremarkable, and the physical examination is normal.

Questions

1. What are the proposed benefits of newborn screening?
2. Which newborn screening tests are most commonly performed?
3. How are the results of newborn screening tests reported to physicians?
4. How should a patient with an abnormal newborn screening result be managed?
5. What are the most common causes of false-positive and false-negative results?
6. What are the ethical issues and future challenges surrounding newborn screening?

Newborn screening programs are designed to identify neonates at risk for catastrophic outcomes from treatable illnesses. Technologic advances in the past 50 to 60 years, such as tandem mass spectrometry, have made it possible to test for more than 50 metabolic disorders from a single blood spot. New techniques in molecular biology, including high-throughput DNA sequencing, allow for rapid diagnostic testing of conditions such as cystic fibrosis.

From the inception of newborn screening in the 1960s until 2005, each state in the United States chose a different set of conditions for its newborn screening program, based on disease prevalence, cost, availability of treatment, and false-positive rates. In 2005, an expert panel from the American College of Medical Genetics and Genomics recommended 29 core disorders for which newborn screening was most effective, as well as 25 secondary disorders that are in the differential diagnosis of a core disorder. In 2010, severe combined immunodeficiency (SCID) was added to the core list. Screening for critical congenital heart disease (by pulse oximetry) was endorsed by the American Academy of Pediatrics in 2011. By the end of 2013, all states offered testing for the 29 original core disorders, although screening for secondary disorders and SCID was variable.

Since 2015, development of federal recommendations for newborn screening has been the responsibility of the Advisory Committee on Heritable Disorders in Newborns and Children (under the US Department of Health and Human Services). The conditions on the Recommended Uniform Screening Panel include metabolic disorders, hemoglobinopathies and thalassemias, congenital hypothyroidism, SCID, hearing screening (see Chapter 88), and critical congenital heart disease. Advances in treatment (eg, enzyme replacement therapy) have resulted in recent expansion of the panel. As of July 2018, the latest additions to the Core Conditions list were disease type II (ie, Pompe disease), mucopolysaccharidosis type I (ie, Hurler syndrome), X-linked adrenoleukodystrophy, and spinal muscular atrophy (caused by homozygous deletion of exon 7 in *SMN1*; Table 25.1). The Recommended Uniform Screening Panel also has a list of Secondary Conditions, based on the earlier recommendations (Box 25.1).

Primary care physicians have 3 crucial roles in newborn screening. First, they provide education to parents about the newborn screening process. Second, they ensure that specimens are drawn under proper circumstances and that the results are promptly followed up. Finally, they provide medical follow-up and referral in cases of positive test results. All physicians must have contact information for state newborn screening programs and local pediatric subspecialists. Contact information for these groups is listed in Table 25.2.

Epidemiology

More than 4 million newborns are screened each year in the United States. The National Newborn Screening 2006 Incidence Report shows that newborn screening identifies 1 in 3,200 newborns with a metabolic disorder, 1 in 2,200 with congenital hypothyroidism, 1 in 2,200 with sickle cell disease or a related hemoglobinopathy, and 1 in 29,000 with congenital adrenal hyperplasia. Several disorders are more common in particular ethnic groups. For example, cystic fibrosis has an incidence of 1 in 2,500 in whites, and sickle cell disease has an incidence of 1 in 400 in blacks.

Clinical Presentation

Most neonates with disorders detected on newborn screening are clinically asymptomatic in the first 2 weeks after birth, but others may have significant signs and symptoms (see Table 25.1). The

Table 25.1. Recommended Uniform Screening Panel Core Conditions[a]

Type of Disorder	*Core Condition*	*Possible Signs and Symptoms in Neonates*
Metabolic: Organic acid	Propionic acidemia	Lethargy, vomiting, hypoglycemia, ketoacidosis, hyperammonemia, neutropenia, thrombocytopenia
	Methylmalonic acidemia (ie, methylmalonyl-CoA mutase) Methylmalonic acidemias (ie, cobalamin disorders)	Same as above
	Isovaleric acidemia	Lethargy, vomiting, odor of sweaty feet, hyperammonemia
	3-Methylcrotonyl-CoA carboxylase deficiency	Lethargy, vomiting; may be asymptomatic[b]
	3-Hydroxy-3-methylglutaricaciduria	Lethargy, vomiting, hypoglycemia, hyperammonemia, elevated transaminases
	Holocarboxylase synthetase deficiency	Lethargy, vomiting, hypoglycemia, ketoacidosis, hyperammonemia
	β-Ketothiolase deficiency	Lethargy, vomiting; may be asymptomatic[b]
	Glutaric acidemia type 1	Macrocephaly possible; otherwise asymptomatic[b]
Metabolic: Fatty acid oxidation	Carnitine uptake defect/carnitine transport defect	Lethargy, cardiac decompensation, hypotonia, hypoglycemia, liver dysfunction; may be asymptomatic[b]
	Medium-chain acyl-CoA dehydrogenase deficiency	Lethargy, coma, sudden death, hypoglycemia, liver dysfunction, arrhythmias, symptoms similar to those of Reye syndrome; may be asymptomatic[b]
	Very-long-chain acyl-CoA dehydrogenase deficiency	Lethargy, cardiac decompensation, coma, sudden death, hypoglycemia; may be asymptomatic[b]
	Long-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency	Lethargy, cardiac decompensation, hypoglycemia, liver dysfunction; may be asymptomatic[b]
	Trifunctional protein deficiency	Same as above
Metabolic: Amino acid	Argininosuccinicaciduria	Lethargy, vomiting, seizures, coma, hyperammonemia
	Citrullinemia type I	Lethargy, vomiting, seizures, coma, hyperammonemia
	Maple syrup urine disease	Lethargy, vomiting, seizures, coma, maple syrup odor
	Homocystinuria	Asymptomatic[b]
	Classic phenylketonuria	Asymptomatic[b]
	Tyrosinemia type I	Vomiting, diarrhea, liver dysfunction (jaundice, bleeding, hypoglycemia), boiled cabbage odor; may be asymptomatic[b]
Endocrine	Primary congenital hypothyroidism	May be asymptomatic[b]; umbilical hernia, enlarged fontanelle, macroglossia, jaundice
	Congenital adrenal hyperplasia	Virilization in females, salt-wasting crisis
Hemoglobin	SS disease (ie, sickle cell anemia)	Asymptomatic[b], dactylitis
	S β-thalassemia (ie, sickle β-thalassemia)	Asymptomatic[b]
	SC disease (ie, hemoglobin C sickle cell disease)	Asymptomatic[b]
Other	Biotinidase deficiency	Lethargy, hypotonia, seizures; may be asymptomatic[b]
	Critical congenital heart disease	Hypoxemia
	Cystic fibrosis	Meconium ileus, intestinal obstruction
	Classic galactosemia	Lethargy, vomiting, diarrhea, jaundice, hepatomegaly, cataracts, sepsis (*Escherichia coli*)
	Glycogen storage disease type II (ie, Pompe disease)	Hypotonia, hypertrophic cardiomyopathy; may be asymptomatic[b]
	Hearing loss	Deafness, speech delay

(continued)

Table 25.1. Recommended Uniform Screening Panel Core Conditions[a] (*continued*)

Type of Disorder	*Core Condition*	*Possible Signs and Symptoms in Neonates*
Other (*continued*)	Severe combined immunodeficiencies	Recurrent infections
	Mucopolysaccharidoses type I	Inguinal hernia, upper respiratory tract infection; may be asymptomatic[b]
	X-linked adrenoleukodystrophy	Asymptomatic[b]
	Spinal muscular atrophy caused by homozygous deletion of exon 7 in *SMN1*	Impaired motor function

Abbreviations: CoA, coenzyme A; *SMN1*, survival of motor neuron 1.

[a] As of July 2018.

[b] Asymptomatic covers the first month after birth and does not exclude very rare case reports of neonatal presentations.

Adapted from Advisory Committee on Heritable Disorders in Newborns and Children. Recommended Uniform Newborn Screening Panel Core Conditions (as of July 2018). Washington, DC: U.S. Department of Health & Human Services; 2018 www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/rusp-uniform-screening-panel.pdf.

Box 25.1. Recommended Uniform Screening Panel Secondary Conditions[a]

Organic Acid Disorders
- Methylmalonic acidemia with homocystinuria
- Malonic acidemia
- Isobutyrylglycinuria
- 2-Methylbutyrylglycinuria
- 3-Methylglutaconicaciduria
- 2-Methyl-3-hydroxybutyricaciduria

Fatty Acid Oxidation Disorders
- Short-chain acyl-CoA dehydrogenase deficiency
- Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency
- 2,4-Dienoyl-CoA reductase deficiency
- Carnitine palmitoyltransferase type I deficiency
- Carnitine palmitoyltransferase type II deficiency
- Carnitine acylcarnitine translocase deficiency

Amino Acid Disorders
- Argininemia
- Citrullinemia type II
- Hypermethioninemia
- Benign hyperphenylalaninemia
- Biopterin defect in cofactor biosynthesis
- Biopterin defect in cofactor regeneration
- Tyrosinemia type II
- Tyrosinemia type III

Hemoglobin Disorders
- Various other hemoglobinopathies

Other Disorders
- Galactoepimerase deficiency
- Galactokinase deficiency
- T-cell related lymphocyte deficiencies

Abbreviation: CoA, coenzyme A.

[a] As of July 2018.

Adapted from Advisory Committee on Heritable Disorders in Newborns and Children. Recommended Uniform Newborn Screening Panel Secondary Conditions (as of July 2018). Washington, DC: U.S. Department of Health & Human Services; 2018 www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/rusp-uniform-screening-panel.pdf.

presence of such features may require a more urgent work-up or even hospitalization. Unfortunately, severe forms of some metabolic disorders may cause coma and encephalopathy by 48 hours of age. In these cases, newborn screening results are critical, because they will suggest a probable diagnosis and allow early optimization of therapy.

Differential Diagnosis

Although newborn screening techniques are continually improved, false-positive and false-negative results may occur. Mislabeled specimens, technical errors, and reporting errors can occur in any laboratory. Any specimen collected before 12 hours of age is at risk for a false-negative metabolic result or a false-positive hypothyroidism result. Preterm newborns have a reduced metabolic capacity and therefore may exhibit higher metabolite levels compared with levels in full-term infants, which can produce false-positive results. Anemia or polycythemia can affect the amount of plasma per blood spot, which may lead to false-negative results. Transfusion may alter galactosemia and hemoglobinopathy testing. Neonates receiving hyperalimentation may have increased amino acid and lipid levels, especially if the newborn screen is drawn from a central line (rather than a heel stick). To ensure accurate and uniform testing and interpretation, it is imperative that relevant clinical information be included when the newborn specimen is submitted.

Newborn Screening Practices

Parental Education and Consent

All parents should be informed of the state screening program at the prenatal visit or during the initial newborn examination. Written materials that explain the screening program are available from state screening offices. Health professionals are responsible for educating parents on the method for obtaining the blood specimen, the risks and benefits of screening tests, conditions on the screening panel, and the implications of positive results.

It is important to tell the parent or parents that a positive result does not necessarily mean that the newborn has a particular

Table 25.2. Contact Information for State Newborn Screening Programs and Local Pediatric Subspecialists

Contact Type	*Organization*	*Website*
State newborn screening programs	National Newborn Screening and Global Resource Center	http://genes-r-us.uthscsa.edu
Geneticists: metabolic and clinical	Society for Inherited Metabolic Disorders	www.simd.org
	American College of Medical Genetics and Genomics	www.acmg.net
Pediatric endocrinologists	Pediatric Endocrine Society	www.pedsendo.org
Pediatric hematologists	American Society of Pediatric Hematology/ Oncology	www.aspho.org
Pediatric pulmonologists	Cystic Fibrosis Foundation	www.cff.org

disorder. Results must be confirmed by more specific tests. In addition, the parent or parents should be advised that in some children disorders are missed because of sampling errors, faulty testing, or inadequate accumulation of the abnormal metabolite at the time of testing.

Newborn screening is mandatory in all states, although many states allow exemptions for religious beliefs or other reasons. In most states, parents have given verbal informed consent when practitioners have discussed the state-mandated program with them and the parents have agreed to participate. A few states require signed consent to opt into the newborn screening program, and several more require consent to disclose identifiable information. Physicians should document parental refusal regardless of state laws.

Specimen Collection and Handling

Proper specimen collection and handling are essential components of a successful screening program. All newborns should be screened before discharge from the hospital, ideally between 24 and 48 hours of age. Screening too early increases the chance of a false-negative metabolic result or a false-positive hypothyroidism result. For this reason, some states have a mandatory second screen between 1 and 6 weeks of age, whereas others require a second screen only if the first screen is obtained before a specified time (eg, 12 hours, depending on the state). Late screening increases the sensitivity of metabolic testing but also increases the risk for delayed diagnosis of a life-threatening condition, such as galactosemia. If possible, blood samples should be obtained prior to any transfusions or dialysis. If not possible, screening should still be performed as outlined previously, and arrangements should be made to repeat the screen at an appropriate time.

Several drops of blood are needed to fill each circle on the newborn screening filter paper, and the sample must saturate the paper evenly. The use of needles and glass capillary tubes for blood collection is discouraged, because they may cause hemolysis or microtears in the filter paper. Specimens must be individually air-dried in a horizontal position to avoid contamination and excessive exposure to heat. They should be mailed or preferably, sent by courier, to the laboratory within 24 hours of collection. Inadequate specimen collection and handling can result in test inaccuracies, delays in reporting results to physicians, and unnecessary repetition of screening tests. Therefore, all individuals who are involved in the newborn screening process should strictly adhere to the procedures set forth by their state program.

Reporting of Results

In most states, all results of neonatal screening tests, whether normal or abnormal, are reported to the physician of record. Normal results are mailed to the physician for placement in the patient's medical record. Abnormal results are usually reported by telephone or letter, depending on the severity of the potential condition. Results are also sent to the hospital in which the neonate was born for inclusion in the medical record. The physician of record is responsible for contacting the parent or parents about the need for confirmatory testing and, if necessary, referral to an appropriate subspecialist. If a newborn is no longer under the care of this physician or if the family cannot be located, state and local public health departments can assist in the search for the newborn and family.

Diagnostic and Therapeutic Considerations

A health care team consisting of a primary care physician and staff, state newborn screening office personnel, state newborn screening laboratory, local laboratories, and a subspecialty physician is responsible for care and follow-up of patients with positive newborn screening results. All newborns with abnormal results, whether borderline or clearly significant, should be evaluated by their primary care physician. A complete patient history and physical examination as well as a family history should be obtained. Positive results for newborn screening tests often normalize on follow-up testing or on a second screen. Therefore, most follow-up evaluations focus on targeted diagnostic tests. Depending on the nature of the suspected disorder, initiation of treatment before confirmatory laboratory results are known may be appropriate. For example, prophylactic antibiotics should be administered if sickle cell anemia is suspected. After confirmatory results have been received, the treatment can be modified or halted.

Potentially life-threatening conditions in the newborn period, such as galactosemia, maple syrup urine disease, and congenital adrenal hyperplasia, are particularly important to evaluate and treat emergently. Depending on the clinical picture, suspected disorder, and experience of the physician, telephone consultation with a specialist or immediate referral to a regional medical center may be necessary.

Almost all of the diseases in the current newborn screening panel are inherited in an autosomal recessive manner. Families of affected newborns should be offered genetic counseling for future pregnancies, in addition to written information about the newly diagnosed condition. Depending on the condition, it may be necessary to evaluate older siblings. For some conditions, such as 3-methylcrotonyl coenzyme A carboxylase deficiency, a positive newborn screen may be indicative of an affected asymptomatic mother, whose circulating metabolites are also present in the blood of her newborn.

Current Issues and Future Challenges

Protecting patient privacy is of utmost importance, and most programs have laws to protect a patient's personal information, blood spots, and genetic information. Great concern exists among parents and physicians that insurance companies will use newborn screening information to discriminate against children and their families.

It is indisputable that newborn screening saves lives. Additionally, from a purely economic standpoint the cost of newborn screening programs is outweighed by the resulting reduction in morbidity and mortality. However, some diseases that are now on the Recommended Uniform Screening Panel, such as lysosomal storage disorders, have extremely costly treatments that may total millions of dollars over the lifetime of the patient and produce significant morbidity. Cost-benefit analyses will be crucial to shaping future newborn screening panels. Pediatricians and other health professionals must advocate for insurance coverage for newborn screening panels, especially as hospital charges for newborn testing increase.

Several newborn screening tests may detect asymptomatic carrier status in newborns. Although knowledge of a patient's carrier status may be of some use for childbearing decisions, it has no immediate benefit for the newborn and may inadvertently result in discrimination and stigmatization. The parents of affected newborns, who usually are asymptomatic carriers, are presented with the same dilemma and may wish to forego additional testing concerning their own carrier status.

New challenges will emerge as genetic technology advances toward the idea of using genomic sequencing as the standard test for newborn screening. The thought that genomic sequencing could someday be applied to all newborns seems less remote today than it did a few years ago, judging by statements in published reviews. The technical feasibility, ethics, legal questions, and medical outcomes of genomic testing remain topics for dialogue and research. Health professionals may refer to current medical literature to stay abreast of this interesting and developing area.

CASE RESOLUTION

The patient should undergo a full evaluation, including an electrolyte panel, because of the possibility of salt-wasting congenital adrenal hyperplasia. Confirmatory testing, including measurement of precursor hormones such as 17α-hydroxyprogesterone and subsequent molecular testing, as well as glucocorticoid therapy should be considered in consultation with a pediatric endocrinologist.

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CHAPTER 26

Caring for Twins and Higher-Order Multiples

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CASE STUDY

An expectant mother visits you. She has been advised by her obstetrician that a sonogram shows she is pregnant with twins. She asks about care of twins and what special considerations she should keep in mind as she looks forward to the delivery. In particular, she is concerned about the feeding schedule and whether she will be able to breastfeed.

Questions

1. What is the incidence of twin births?
2. What is the difference between fraternal and identical twins?
3. What major medical problems may affect twins and higher-order multiples?
4. What developmental and behavioral problems are associated with raising twins?

With the advent of artificial reproductive therapy 40 years ago, the incidence of twins and higher-order multiples has increased. Counseling the parents of multiples provides a unique opportunity for pediatricians. Much of what is known about caring for multiples comes from work with twins.

Parents of multiples often have many questions about the care of their children, but they rarely pose them to health care professionals. In a study in which 18 out of 29 mothers breastfed their twins, only 3 received information about breastfeeding from their physicians. One mother had been told by her obstetrician that she could not breastfeed her twins. Physicians should become knowledgeable about caring for multiples and the unique challenges they present to parents related to feeding, sleeping, and behavior.

Epidemiology

On July 25, 1978, Louise Brown was the first baby born as a result of in vitro fertilization (IVF). Since then, improved prenatal care and IVF methods have contributed to the increase in multiple births. According to the American Society for Reproductive Medicine, the rate of twins has increased more than 75% over the last 40 years in the United States. Twin rates have also increased in Finland, Norway, Austria, Sweden, Australia, Hong Kong, Japan, Canada, Singapore, and Israel, with the highest rate increase in Nigeria. A major contributor to the increase in multiple births is that women are starting their families later than in previous generations. The Centers for Disease Control and Prevention reports that from 1980 to 2009, twin birth rates increased 76% for women aged 30 to 34 years, nearly 100% for women aged 35 to 39 years, and more than 200% for women aged 40 years and older.

Because of the increased risk of infertility with advanced maternal age, more couples are choosing to conceive with assisted reproductive technologies, including ovulation-stimulating drugs, IVF, and intracytoplasmic sperm injection. More than one-third of twins and more than three-quarters of triplets and higher-order multiples in the United States resulted from conception assisted by fertility treatments.

The overall natural prevalence of twin births is about 33 in 1,000. Twins account for just slightly more than 1% of all births, and 20% of neonates born at fewer than 30 weeks' gestation are twins. The average prevalence of monozygotic or identical twins, which is the same for all women regardless of race and age, is about 1 in 300 births. The incidence of dizygotic or fraternal twins varies among different groups and by method of conception. In the United States, blacks and whites have comparable incidences of live-born twin deliveries, and both have significantly higher rates than Hispanic women. A maternal family history of dizygotic twins correlates most strongly with an increased incidence of twins. A family history of monozygotic twins or a paternal family history of dizygotic twins does not increase the likelihood of twins.

Pathophysiology

Higher-order multiples, conceived naturally or via artificial reproductive technology, may be fraternal or a combination of monozygotic twins and fraternal siblings. Monozygotic twins result from the splitting of a single egg. They may share a placenta (monochorionic) (Figure 26.1A and 26.1B) and, in rare cases, may also share an amniotic sac (monoamnionic). When splitting occurs early (after several cell divisions of the zygote), each fetus develops its own

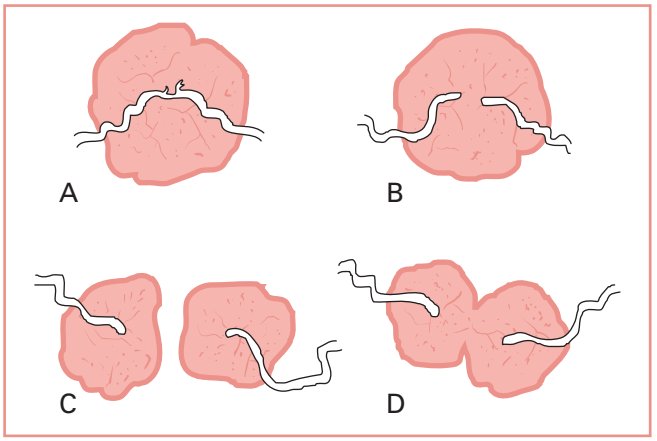

Figure 26.1. Variations in placentas in twin births. A, Monochorionic placenta, cords close together. B, Monochorionic placenta, cords farther apart. C, Dichorionic placentas, separate. D, Dichorionic placentas, fused.

chorion and amnion, leading to dichorionic and diamnionic placentas. Dizygotic twins result from 2 eggs, with each egg fertilized by a different sperm. Dizygotic twins have 2 placentas (Figure 26.1C). Although these placentas may fuse together like 2 pancakes, they are almost always dichorionic and diamnionic (Figure 26.1D). Ultrasonography at 14 weeks or sooner has been found to be 96% predictive of monochorionic twins and can also predict monoamnionic twins, anomalies, and syndromes.

Following birth, many parents want to determine whether twins are monozygotic or dizygotic. Different-sex twins are almost always dizygotic, although monozygotic twins of different sexes have been reported in the literature. This occurs when 1 twin loses a Y chromosome and becomes a phenotypic female with Turner syndrome (XO). Occasionally, the male twin may have an XXY chromosome complement and have Klinefelter syndrome.

To determine whether twins are monozygotic or dizygotic after birth, a number of procedures can be undertaken. Visual or pathological examination of the placenta is helpful. About two-thirds of monozygotic twins have a common chorion and share 1 placenta. Finding a single chorion usually means the twins are monozygotic, unless the placentas of dizygotic twins have fused together. DNA testing is the preferred method for determining zygosity. Most commercially available testing, often referred to as zygosity testing, involves examining DNA obtained from buccal swabs from each child. Identification of short tandem repeats via polymerase chain reaction is typically accurate 99% of the time and is similar to techniques used in forensic medicine. Commercial laboratory charges range from $100 to $200, although prices vary significantly depending on the company and whether zygosity is being tested for twins or higher-order multiples.

Recent research on monozygotic twins has also focused on the effect of epigenetics, or how the environment affects genetics. By analyzing the DNA of monozygotic twins, researchers are hoping to identify epigenetic tags that mark a change in gene expression. Although DNA cannot be altered, DNA methylation, which affects the strength of gene expression, may be a process that, in the future, can be manipulated to reverse some complex disorders, such as autism spectrum disorder.

Differential Diagnosis

Diagnosing multiples is not difficult, but physicians should be aware of the problems these newborns may experience.

Perinatal Complications

Multiple births are associated with a significantly higher risk of perinatal complications relative to singleton births. The maternal complication most commonly reported with multiples is pregnancy-induced hypertension. Maternal preeclampsia rates are higher in twins and increase nearly 5-fold with triplets. In addition, mothers of twins who conceived via IVF have a higher rate of preeclampsia than mothers of twins who conceived naturally. Other maternal complications include placenta previa, antepartum hemorrhage, gestational diabetes mellitus, anemia, uterine atony, and maternal death.

Monozygotic twins are at increased risk for death and cerebral palsy because of complications such as severe birth weight discordance and twin transfusion syndrome (TTS). Twin transfusion syndrome is seen in 10% to 15% of monochorionic pregnancies and results from unbalanced blood flow due to vascular anastomoses within the shared placenta. The diagnosis is suspected by ultrasound when 1 fetus is growth restricted with oligohydramnios and the other fetus has evidence of volume overload with polyhydramnios. Both twins are ultimately at risk for fetal hydrops or death. Without treatment, TTS-induced death of at least 1 twin is as high as 80% to 100%. Of additional concern, the death of 1 twin is associated with neurologic damage or subsequent death of the surviving twin, with 1 in 10 surviving twins developing cerebral palsy.

Until recently, treatment was drainage of amniotic fluid in the twin with polyhydramnios to reduce the risk of preterm delivery. Endoscopic laser ablation of placental anastomoses has emerged as the treatment of choice for severe TTS pregnancies diagnosed and treated prior to 26 weeks' gestation. Laser ablation addresses the primary pathology and results in an average gestation at delivery of 33 weeks, which is a significant improvement from the average 29 weeks with serial amniotic fluid reductions. Laser ablation is not without risks, however; reported complications include premature rupture of membranes, amniotic fluid leakage into the maternal peritoneal cavity, vaginal bleeding, and chorioamnionitis.

One percent of monozygotic twins are monochorionic–monoamnionic. Although monoamnionic twins have a lower risk of TTS, they are at very high risk for cord accidents. Monoamnionic pregnancies are monitored closely, and once the fetuses reach viability, emergent delivery is indicated if fetal distress is noted to avoid fetal death. Because fetal death significantly increases the risk of cerebral palsy and other neurologic disorders in the surviving twin, it is no longer recommended to allow fetal death in 1 monoamnionic twin to lengthen the gestation of the non-distressed twin.

Congenital Malformations

Twins and higher-order multiples have an increased risk of anomalies. Monochorionic twins have a higher risk of cardiac anomalies than dichorionic twins, increasing their need for fetal echocardiograms. Multiples conceived via IVF or intracytoplasmic sperm

injection have increased risk for anomalies and aneuploidy. Disorders of genetic imprinting (eg, Beckwith-Wiedemann syndrome, Angelman syndrome) are also increased with intracytoplasmic sperm injection. These genetic complications are thought to be secondary to the underlying cause of infertility instead of artificial reproductive technologies. Because the costs associated with infertility treatments are substantial, many couples choose not to obtain a comprehensive chromosomal analysis looking for deletions or translocations on themselves prior to using reproductive technologies. Nuchal translucency and chorionic villus sampling can be used to detect and confirm suspected aneuploidy as early as the first trimester.

In addition to increased risks of malformations, multiples are at risk for deformations secondary to crowding, including torticollis, hip dislocation, plagiocephaly, and foot deformities. Monochorionic twins are also at risk for becoming conjoined twins, estimated to occur in 1 in 50,000 to 200,000 gestations, with more than 50% dying in utero or being stillborn and 35% dying within the first 24 hours after birth. Although monochorionic twins are more commonly males, conjoined twins are often female. Conjoining occurs because of incomplete splitting of the embryo or after a secondary fusion between 2 previously separate embryos. Prenatal ultrasonography is commonly used to diagnose this condition; more recently, prenatal magnetic resonance imaging has been used to evaluate specific anomalies. Due to surgical advances, some parents continue the pregnancy with hopes the live-born neonates can be separated.

Postnatal Complications

Approximately 60% of twins and 90% of triplets are born preterm, increasing the risk of morbidity and mortality. On average, most single pregnancies last 39 weeks, twin pregnancies 36 weeks, triplets 32 weeks, quadruplets 30 weeks, and quintuplets 29 weeks. The most common cause of preterm delivery in these neonates is premature rupture of membranes.

Although growth in twins tends to be normal until 30 to 34 weeks' gestation, growth restriction is commonly associated with multiple births. Twins conceived by IVF are more likely to be born at a low birth weight than spontaneously conceived twins. Smaller twins have an increased incidence of hypoglycemia in the newborn period and have higher rates of targeted learning deficits and school failures during childhood. In addition, children born with growth restrictions have an increased risk for obesity and diabetes in later life. Selective intrauterine growth restriction (IUGR), when only 1 twin is affected by IUGR, occurs in 10% of monochorionic twins. This occurs when the twin with IUGR has reversed flow or persistent absent flow in the umbilical artery.

Neonatal mortality is 4-fold higher in twins and 15-fold higher in higher-order multiples. Neonatal morbidity is much higher in multiple births because of the increased incidence of preterm birth and growth restriction. The risk of these complications increases with the number of fetuses. The perinatal mortality of monozygotic twins is 8 times that of singletons and 4 times that of dizygotic twins. Twins and higher-order multiples are also at increased risk for cerebral palsy.

Evaluation

History

A general medical history should be obtained, including a history of the pregnancy. Any specific medical concerns should also be addressed (Box 26.1).

Physical Examination

The initial evaluation of newly born twins involves assessment of gestational age and determination of the presence of any medical problems or anomalies (see Chapter 23). Older twins may undergo health supervision visits at which routine as well as specific concerns are addressed.

Laboratory Tests

Newborns should be assessed for the presence of anemia or polycythemia with a hemoglobin level determination. Hypoglycemia may occur in the newborn period and should be assessed frequently until glucose levels are stable. If the twins are preterm, they may have many of the problems seen in singleton preterm newborns, such as neonatal respiratory distress syndrome and necrotizing enterocolitis.

Older children should receive an appropriate evaluation for age, with a specific focus on any behavioral concerns.

Management

The focus of the management of multiples involves counseling parents about issues related to routine care and anticipated stress of caring for more than 1 newborn simultaneously. Parents often care for 2 or more children at the same time, but multiples present unique issues related to multiple children who are developmentally and chronologically at the same point. Many parents experience anxiety about the upcoming challenges they will face. Baby care books that specifically discuss birthing and raising multiples are available. Support groups and websites also provide information for families of multiples.

Feeding multiple newborns is often an exhausting challenge for parents, and consultation with a lactation expert is recommended. The physical demands of feeding multiple newborns are often compounded by women recovering from prenatal complications such as preeclampsia. Because preterm birth is common, newborns may have an immature suck reflex, making feeding more challenging. Few multiples are still exclusively breastfed by 4 months of age, and common reasons cited for unsuccessful breastfeeding of multiples

Box 26.1. What to Ask

Caring for Twins

- Did the mother have any problems during the pregnancy?
- How long did the pregnancy last?
- Did the mother take any medications, including fertility drugs?
- Did the children have any problems after the delivery or in the newborn nursery?

include maternal stress, depression, fatigue, perceiving they were producing insufficient milk, and time burden. Despite these obstacles, parents should know that breastfeeding is possible even for triplets and understand the benefits of breastfeeding to the newborns' health. It is recommended that mothers begin breastfeeding as soon as possible to establish their milk supply. An electric pump is a useful adjunct to help establish and continue breastfeeding. If supplemental nutrition is needed, utilizing a medicine dropper, syringe, spoon, cup, or finger feeding instead of a bottle will reduce the risk of newborns developing a preference for an artificial nipple.

Some options for breastfeeding are outlined in Box 26.2.

Sleeping in the same crib is no longer recommended because of concerns about co-sleeping. Approximately 3,500 babies die from sleep-related deaths per year. Although co-sleeping is not recommended, room sharing, in which infants sleep in the same room as parents, is recommended for infants 6 to 12 months of age.

Travel can be challenging with twins and higher-order multiples. Planning ahead is the key to making this a positive and constructive experience. Having a separate diaper bag in each car and additional car seat adapters may make travel easier, but safety should never be compromised. It is important to counsel parents about car safety seats. Parents who cannot afford the cost of multiple car safety seats may resort to placing 1 baby in the car safety seat and the others on the seat of the car, a dangerous practice that is illegal throughout the United States. Parents should be advised of the need for car safety seats for all babies.

In the interest of safety, bathing should be done separately until babies can sit up.

Box 26.2. Breastfeeding Twins and Higher-Order Multiples

1. Position

a. Babies may be put in a number of positions. Regardless of position, it is important to make sure that the baby's head and neck are supported just enough so the baby can adjust its head to breathe during breastfeeding. The mother can be sitting and cradling (across the chest) 1 baby while holding the other like a football. Alternatively, the mother may cradle both babies so that they are cross-positioned over one another with their legs make an X across the mother's lap, or she may have both under her arms in a football position. Breastfeeding pillows designed for feeding multiples are helpful, but several firm pillows are also sufficient.

b. Maternal positions can be sitting up with pillow back support, reclining, or lying down. To help prevent maternal fatigue, reclining and lying down are preferred.

2. Timing of Feeds

a. Feed both babies at the same time, with 1 on each breast. This method is recommended only after adequate breastfeeding has been established in each twin, typically not until after 1 week after birth. It is advised that the baby having fewer problems latching be placed on the breast first so that the milk ejection reflex is already established for the poorer-feeding baby. Because the babies may not drink the same amount, it is important that they feed on the opposite breast for the next feeding to maximize milk production.

b. Feed the babies at different times. The mother breastfeeds 1 and then the other, starting with the more vigorous feeder. This approach may pose a problem; both babies may be hungry at the same time, and maternal fatigue may inhibit success because the chance for sleep is diminished with this method. Some mothers prefer this method because it provides individualized attention and opportunities for attachment with each baby.

c. Breastfeed 1 baby and bottle-feed the other, which gives the mother a free hand. Most parents use a combination of breastfeeding and bottle-feeding. A mother can let the first baby feed on demand but awaken the second when the first is done. Eighty percent of parents of twins acknowledge that they prop the bottle instead of holding it, and they should be counseled against this. There are several effective feeding positions that do not require bottle propping, and parents should be encouraged to adopt 1 of these positions.

3. Higher-order Multiples

Breastfeeding triplets and higher-order multiples is even more challenging than breastfeeding twins. Mothers of triplets exclusively breastfeeding report they feed 2 babies, 1 on each breast, and the third follows on both breasts. Because the hind milk has higher fat content, it is important to rotate the feeding order of the babies. Another popular option is to breastfeed 2 and have the third bottle-feed simultaneously.

4. Maternal Considerations

a. Feeding twins or higher-order multiples may decrease the amount of sleep a mother gets. Because sleep deprivation is associated with maternal depression and exclusively breastfeeding mothers of multiples report more sleep problems compared with mothers who do not breastfeed or who formula-feed and breastfeed, these factors should be discussed when offering feeding options to parents. Encouraging paternal involvement with feeding may alleviate some maternal stress and sleep deprivation.

b. Maternal nutrition plays a key role in quality and quantity of milk produced. Research shows that the higher the nutrition value of the mother's diet, the higher the nutrition quality of her milk. According to the Centers for Disease Control and Prevention, the mother should increase her calorie intake by 450 to 500 kcal per baby per day. In addition, a multivitamin may be recommended.

Toilet training is reportedly easier with some twins because 1 twin learns from the other via modeling or peer pressure.

Maintenance of individuality for multiples may be challenging. Researchers suggest that mothers can bond to only 1 newborn at a time, a concept called *monotropy.* In addition, mothers bond more strongly with the twin who leaves the hospital first. Twins are often dressed alike and given similar names because this may facilitate the bonding process. To help with individual development, physicians are encouraged to obtain history and examine each child individually. Physicians should attempt to distinguish the children from one another independent of parental reminders. Twins should not be referred to as "the twins" but by their respective names. As multiples get older, issues related to classrooms and birthday parties frequently arise, and they should be consulted about their preferences. Individual birthday parties and gifts should be considered, as some multiples comment on their disappointment at receiving the same present for birthdays and holidays. There is no surprise in opening gifts if the other twin opened a gift first.

Whether multiples should be placed in the same or different classrooms is unclear. Placement in different classrooms or schools is advocated to support each child's individual development. However, being in the same classroom ensures the same educational standard and may be more convenient for families. Research is variable on whether separate or same classrooms are better or even make a difference for twins with regard to emotional and academic outcomes. Some studies do suggest that boys do better emotionally when they are together versus separated. It is currently recommended that school districts have a flexible policy addressing school placement of twins. Online resources are available to assist families and schools in determining the best school placement for twins. Families with higher-order multiples are more likely to have children in separate schools because of the higher risk that some of the children will have developmental delays.

Sibling rivalry is common in all families but is different among co-multiples as well as other siblings within a family. Twins are often directly compared to one another, while older siblings may resent the attention paid to the new babies. Because twins often exclude siblings and peers socially, parents are encouraged to schedule times when 1 twin and sibling are with 1 parent and the other twin is alone with another family member. Isolating twins (or 2 triplets from a third) fosters more sibling interaction and less dependency between the twins. These separations are encouraged to begin early in development because the later in development twins are separated, the less agreeable twins are to being apart.

Developmental differences among multiples may also contribute to sibling rivalry. The child who is smaller or more delayed may become jealous of the co-multiple. Conversely, typically developing children may become frustrated when the sibling with special needs receives more attention than they receive. Parents and family should be encouraged to acknowledge and praise individual characteristics of each twin.

Until age 3 years, language and speech development is delayed in twins relative to singletons. A contributing factor to language delay is less time for individual facilitated play, which is helpful for language development. If twins communicate with a private language, they have an increased risk of language and cognitive delays. Language delays usually become much less pronounced by mid-childhood. Attention-deficit/hyperactivity disorder is more common in twins but not as common as language delay. The smaller twin has a higher rate of specific learning deficits and school difficulties. The temper tantrums multiples display can be severe and are understandable given the heightened need to gain parental attention from their sibling. Having twins in the home is a risk factor for child abuse, either to a twin or to their siblings.

The risk of cerebral palsy is increased with higher multiples because of the increased rates of preterm birth and IUGR. Fetal death of a co-multiple and monochorionic placentas are the biggest risk factors for developing cerebral palsy.

The effect on families of twins and higher-older multiples starts prior to delivery and includes higher risk to maternal health as well as anticipatory anxiety. Prior to delivery, parents should be made aware that maternal depression is frequently reported after the birth of multiples. The physical stress of caring for multiple newborns can be overwhelming, and parents often feel isolated at home. The incidence of depression is higher in mothers of twins than of singletons, with sleep deprivation cited as a contributing factor. It is important to suggest that parents of multiples obtain outside aid to decrease fatigue and increase their ability to experience respite even for short periods.

In addition to exhaustion and isolation, the increased financial demands that accompany multiple newborns can strain the parents' relationship. Mothers often have to leave work earlier in the pregnancy than women with singleton pregnancies, adding financial burden, especially if they are single or have other children. The medical costs associated with preterm birth can be substantial. To cover for the loss of income at a time of increasing family expenses, the father is often required to work more hours. This increased occupational stress comes at a time when child care demands at home have increased significantly. Financial burdens are especially difficult with multiples conceived artificially because of the cost associated prior to birth. This may be a contributing factor to why parents of twins conceived artificially have reported less satisfaction than parents of twins conceived naturally.

Grief is another significant contributor to parental depression. Approximately 15% of children from multiple births grow up as a singleton survivor. Birthday celebrations serve as reminders to the parents of the death of the other child. Parents grieving the loss of 1 of their twins have comparable grief to those grieving the loss of a singleton pregnancy. It is imperative that physicians caring for the family acknowledge the parents' grief because family and friends often do not acknowledge the parents' pain if there is a surviving newborn.

Surviving children born preterm or small for gestational age are at increased risk of developmental delays. The stress of raising a child with special needs is also a source of grief because parents mourn the loss of their dreams of having a "normal" child.

Prevention

Regardless if conceived naturally or via artificial reproductive technology, it is impossible to guarantee singletons or higher-order multiples. Nonetheless, a maternal family history of dizygotic births increases the likelihood of higher-order multiples. Artificial reproductive technology often results in higher-order multiples. However, the number of embryos implanted via artificial reproductive technology has decreased following high-profile births of grand multiples that highlighted the financial difficulties placed on families, as well as the increased risk of developmental delays in the children.

Prognosis

Although multiples have a higher prevalence of perinatal and postnatal problems, appropriate anticipatory guidance, routine health maintenance, and treating each child as an individual can help families optimize their children's outcome.

CASE RESOLUTION

The mother is advised that breastfeeding is not only possible but recommended. She is told about the options for timing and positioning of the newborns. The issues of family history and child passenger safety are also discussed, and anticipatory guidance on the potential stress of raising multiples is given.

Resources for Parents

American Society for Reproductive Medicine
www.asrm.org

Baby Center
www.babycenter.com

Center for Loss in Multiple Birth
www.climb-support.org

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CHAPTER 27

Male Circumcision

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CASE STUDY

An expectant mother learns that the sex of her fetus is male. She visits you prenatally. She talks about circumcision in addition to issues related to breastfeeding and car passenger safety. Her husband is circumcised. She is unclear about the medical indications for circumcision and asks your opinion about circumcision in the newborn period.

Questions

1. What are the benefits of male circumcision?
2. What are the indications for circumcision in older children?
3. What are the techniques used to perform circumcision?
4. What are the complications of circumcision?
5. What is the current status of insurance coverage of circumcision?

Male circumcision, a procedure in which the foreskin of the penis is removed, has been performed for more than 6,000 years. It is routinely performed in certain groups, most notably among Jewish and Muslim people. In some other cultures (eg, Australian [Aborigine], Polynesian), circumcision is presumably performed to facilitate intercourse. Circumcision can be viewed as a ritual procedure, but its role as a medical procedure has long been controversial.

The benefits of male circumcision have been debated for years. In the past 20 years, even the American Academy of Pediatrics (AAP) has changed its official position on the medical indications for circumcision. The AAP stated in 1999 and reaffirmed in 2005 that circumcision carried potential benefits, although the procedure was not medically indicated. However, in 2012 the AAP released an updated policy stating that the health benefits of circumcision outweigh the risks of the procedure. This statement was based on a systematic evaluation of peer-reviewed literature that demonstrated preventive health benefits of elective male circumcision, including reductions in the risk of urinary tract infections (UTIs) in the first year after birth, decreased risks of heterosexual acquisition of HIV and other sexually transmitted infections, and a decreased incidence of penile cancer. Additionally, the statement noted that male circumcision does not adversely affect penile sexual function/sensitivity or sexual satisfaction and that complications related to circumcision are infrequent and rarely severe.

Disadvantages of routine circumcision in newborns include expenses associated with the procedure and the risk of complications; however, some analyses have demonstrated that neonatal male circumcision is cost-effective in that it reduces the risk for future disease. The procedure is sometimes criticized as an archaic and maiming ritual. Female circumcision, which may involve clitoridectomy or resection and closure of the labia minora or majora, is infrequently practiced in Western culture and is not discussed in this chapter other than to emphasize that female circumcision has no medical benefit.

Circumcision in newborns has been performed in a routine and preventive manner, much the same way immunizations are administered. Primary care physicians should be aware of the risks and benefits of the procedure to enable them to counsel parents and make referrals to consultants should certain medical conditions arise.

Epidemiology

The prevalence of neonatal circumcision, a procedure that became increasingly popular in the United States in the 1950s and 1960s, once ranged from 69% to 97% depending on cultural mores. In the United States, the procedure is commonly performed during the newborn period, and it is the most common surgical procedure performed in the country. During the past decade, the circumcision prevalence in males aged 14 to 59 years increased from 79% to 81%; specifically, 91% in white males, 76% in black males, and 44% in Hispanic males. The estimated prevalence of circumcision for Australian-born men is 59% (newborn rate estimated 10%–20%); in Canada, 32% of men; and in the United Kingdom, 15% of men. A reported 10% of uncircumcised newborn males ultimately require circumcision as adults because of complications of phimosis and balanitis. Uncircumcised males with diabetes are particularly prone to these complications.

Clinical Presentation

Most often, parents will query their child's pediatrician about the advisability of circumcision, and the newborn will not have any clinical symptoms suggestive of a need for the procedure. Older infants and children in need of circumcision may present with symptoms of phimosis, in which the foreskin balloons out on urination; *paraphimosis*, in which a retracted foreskin cannot be returned to its normal position; or recurrent problems of infection or inflammation of the foreskin (*posthitis*), glans (*balanitis*), or both (*balanoposthitis*).

Pathophysiology

In uncircumcised males, the foreskin adheres to the glans until approximately age 6 years, after which a gradual, normal lysing of the adhesive bands connecting the foreskin to the underportion of the glans occurs. Nonphysiologic phimosis occurs as a result of scarring of the preputial wing. Lysing of adhesions in an attempt to treat the phimosis usually results in additional adhesions. If the foreskin is retracted and remains in that position, paraphimosis occurs.

Differential Diagnosis

The differential diagnosis relates to conditions that may be managed with circumcision, including phimosis, paraphimosis, and infection and inflammation of the penis. Conditions such as hypospadias may be mistaken for a partially circumcised penis, because the condition is associated with absence of the ventral foreskin. A careful patient history will differentiate hypospadias from a circumcision.

Evaluation

History

In cases involving newborns, the history should include the presence of any coagulopathies among family members, which would preclude the performance of circumcision. In older infants and children, the history should include problems related to voiding, such as ballooning of the foreskin or difficulty initiating the urinary stream.

Physical Examination

The physical examination should assess the genitalia, with particular emphasis on determining whether evidence exists of *hypospadias*, in which the urethral orifice is not located at the tip of the glans. In such a situation, circumcision should be delayed because the foreskin is used to reconstruct the urethra. In the patient with phimosis, the degree of phimosis also should be assessed.

Laboratory Tests

Routine laboratory tests are not indicated, although a urinalysis may be obtained in children with a history of a prior UTI. Coagulation studies are appropriate in the case of a family history of a bleeding disorder.

Imaging Studies

Imaging studies are not indicated in most children undergoing circumcision. Such studies are relevant, however, should concern exist that the urogenital anatomy might be abnormal.

Benefits

It has been stated that circumcision facilitates penile hygiene by removing the foreskin, which may serve as a repository for bacteria, smegma, and dirt. Ability to retract the foreskin increases with age (Table 27.1); thus, penile hygiene is easier to achieve in older children. The term *phimosis* refers to inability to retract the foreskin. In male infants beyond the newborn period, phimosis is the major indication for circumcision. Phimosis is normal in children up to approximately 6 years of age but is nonphysiologic if urination results in ballooning of the foreskin, regardless of age. When the retracted foreskin acts as a tourniquet in the mid-shaft of the penis, paraphimosis occurs, preventing the return of lymphatic flow. Paraphimosis is commonly related to traumatic retraction of the foreskin, typically during cleaning or by medical personnel during bladder catheterization. Because of this, parents are no longer advised to retract the foreskin in an effort to lyse adhesions. The incidence of paraphimosis is increasing in adults secondary to body piercing. Newly placed penile rings can cause pain sufficient to prevent foreskin retraction.

Table 27.1. Ability to Retract the Foreskin in Boys, by Age

Age	*Percentage With Retractable Foreskin*
Birth	4
6 months	15
1 year	50
3 years	80
6 years	90

Balanitis, or inflammation of the glans, is not uncommon in infants. It is frequently associated with *Candida* infection, and the glans is swollen and erythematous. Posthitis, or inflammation of the foreskin, is also often secondary to *Candida* infection. Other organisms, including gram-negative microbes, may be associated with balanitis. The presence of recurrent balanitis is an indication for circumcision. In older males, indications for circumcision include phimosis, paraphimosis, balanitis, posthitis, and balanoposthitis.

Urinary tract infections reportedly occur 10 times more often in uncircumcised infants than circumcised infants (1 in 100 and 1 in 1,000, respectively). In young uncircumcised boys, UTIs are directly related to colonization of the foreskin with urotoxic organisms. Pyelonephritogenic, fimbriated *Escherichia coli* bind to the inner lining of the foreskin within the first few days after birth. Other bacteria preferentially bind to this mucosal surface, including fimbriated strains of *Proteus mirabilis* and nonfimbriated *Pseudomonas, Klebsiella,* and *Serratia* species. According to several studies, the rate of UTIs has increased as the rate of circumcision has. A 2012 meta-analysis of 22 studies examining the incidence of UTIs in males found a 23% lifetime risk of UTI in uncircumcised males compared with 8.8% in circumcised males. Thus, the lifetime risk of UTI markedly exceeded the 1.5% circumcision complication rate; most of these complications were minor. Complications associated with UTIs have been reported, in particular, bacteremia, meningitis, and death.

The annual incidence rate of penile cancer is 0.58 per 100,000 men in the United States but is 2.9 to 6.8 per 100,000 men in Brazil. These regional differences are thought to be related to lack

of circumcision of the penis. Only a few isolated cases of cancer of the penis occur in circumcised men. Phimosis is strongly associated with invasive penile cancer, with other cofactors such as human papillomavirus (HPV) infection and poor hygiene possibly contributing. Smoking is consistently associated with penile cancer and is further reason to strongly advocate for smoking cessation programs.

Cervical carcinoma among the partners of uncircumcised men is increasingly being reported. In addition, current partners of circumcised men with a history of multiple sexual partners have a lower risk of cervical cancer than partners of uncircumcised men. Circumcision in adolescent boys and men in Uganda was associated with a marked decreased incidence of HPV and human herpesvirus 2 infection. Circumcision has also been associated with a reduced risk for HIV infections. Three randomized, controlled trials conducted in South Africa, Kenya, and Uganda confirmed the findings of observational studies that circumcision is protective against HIV infection. In addition, circumcision was not associated with increased HIV risk behavior. Based on these findings, in 2007 the World Health Organization stated that male circumcision should be part of a comprehensive strategy for HIV prevention. Since the World Health Organization made this recommendation, nearly 15 million voluntary male circumcision have been performed for HIV prevention in 14 countries of eastern and southern Africa, which is estimated to help prevent more than 500,000 new HIV infections through 2030. It remains critical, however, to promote the practice of safe sex, because circumcision confers only partial protection against HPV, human herpesvirus 2, and HIV.

Risks

Risks related to circumcision are related to complications of the procedure (Box 27.1) and are discussed in the Management section of this chapter. Elective circumcision should be performed only if the newborn is stable and healthy.

Parental Counseling

Parents of Newborns

In the newborn period, proper counseling of parents is important, including a discussion of the risks and benefits of circumcision. Opponents to neonatal circumcision cite psychological trauma to neonates from such a painful procedure. Local anesthesia minimizes this effect. Parents should be informed about the benefits of circumcision, including a reduction in the occurrence of UTIs, sexually transmitted infections, and cancer of the penis and cervix. Problems related to the foreskin itself, such as phimosis, paraphimosis, posthitis, and balanitis, also should be discussed.

It is appropriate to tell parents that boys who are not circumcised in the neonatal period may need to be circumcised later in life. Parents should be informed about the risks associated with circumcision in newborns, which are discussed later in the chapter. In older individuals, risks of circumcision include hemorrhage, infection, and injuries to the penis and urethra. In addition, parents should be informed that approximately 2% of circumcised neonates require a second circumcision because of inadequate foreskin removal during the first procedure.

Research has shown that parents are more influenced by the circumcision status of the father, religion, and ethnicity than by physician attitude concerning their ultimate decision about circumcision. The 2012 AAP policy statement emphasizes that parents should consider health benefits and risks in conjunction with their own religious, cultural, and personal preferences, because the medical benefits alone may not outweigh these other considerations for individual families. Counseling during the second trimester of pregnancy results in no change in parents' decision about circumcision. Parents of newborn boys should be instructed in the care of the penis at the time of discharge from the newborn hospital stay, regardless whether the newborn is circumcised.

Parents of Infants and Older Children

The need for circumcision in male infants who present with UTIs is problematic. Patient evaluation involves an attempt to determine the existence of other conditions that may predispose the patient to a UTI. Investigators disagree on the need for circumcision after an initial UTI in uncircumcised boys. No evidence definitively indicates that circumcision at this time decreases the incidence of future UTIs; thus, the decision whether to circumcise is based on parental preference rather than medical evidence. In children who present with significant phimosis or paraphimosis, circumcision is usually recommended to prevent recurrence of these problems. Medical management, including the use of topical steroids for phimosis, may obviate the need for surgery in some children. Such treatment involves the daily external application of betamethasone cream from the foreskin tip to the corona glandis for 4 to 6 weeks. If the frenulum is tight and tearing, local anesthetic can be applied and the frenulum can be transected. Patient history, including the duration of symptoms and whether the child has had similar episodes in the past, helps in formulating appropriate management.

Management

The medical attitude toward circumcision has changed in the past 40 years, with an initial inclination toward circumcision, followed by a move away from circumcision. The present position on circumcision as described by the AAP Task Force on Circumcision suggests that

Box 27.1. Complications Associated With Circumcision

- Bleeding
- Inclusion cysts
- Infection
- Meatal stenosis
- Meatitis
- Penile cyanosis
- Penile lymphedema
- Penile necrosis
- Phimosis
- Repeat circumcision
- Skin bridges
- Urethrocutaneous fistulae
- Urinary retention
- Wound dehiscence

newborn circumcision has potential medical benefits and advantages as well as disadvantages and risks. When circumcision is considered, benefits and risks should be explained to parents, and informed consent should be obtained. Parents should be advised that third-party payers may deny payment for circumcisions, particularly for routine circumcisions in the newborn period.

Contraindications

Circumcisions should be performed only in completely healthy neonates. Contraindications to circumcision are well defined. Any abnormalities of the penis, such as hypospadias, absence of any portion of the foreskin, or chordee, preclude circumcision. Atypical genitalia and preterm birth are contraindications as well. Circumcision should be delayed in preterm and ill term newborns until they are ready for discharge from the hospital. Patients with a personal or family history of bleeding diathesis should not be circumcised. Newborns from such families should be assessed for evidence of coagulation problems and, if present, circumcision should not be performed.

Circumcision Procedure

Numerous techniques are used to perform circumcisions. These procedures may involve clamp techniques with the Gomco clamp, Mogen clamp, or Plastibell device. Any of these techniques is believed to give comparable results when performed by trained, experienced operators. Formal surgical excision also may be performed, usually in older children and adults. Three guidelines should be followed to reduce the incidence of complications: marking of the coronal sulcus in ink, dilation of the preputial wing, and retraction of the foreskin so that the urethral meatus is visualized to prevent cutting the meatus. Electrocautery should never be used in conjunction with metal clamps because of the danger of extensive injury.

Appropriate anesthesia in newborns undergoing circumcision is the standard of care. The pain and stress of circumcision is evidenced by changes in neonate state and behavior. Non-pharmacologic techniques, such as positioning and sucrose pacifiers, are insufficient to prevent procedural pain but may be used in conjunction with other forms of analgesia. Local anesthesia is the preferred method of pain management. *Dorsal penile nerve block*, which involves the subcutaneous injection of a local anesthetic agent at the base of the penis, is effective in reducing pain responses during circumcision. *Ring block*, which involves subcutaneous circumferential injections of a local anesthetic agent around the mid-shaft of the penis, has also been shown to be effective and avoids the potential complication of injecting local anesthesia toward the dorsal vessels. Topical application of lidocaine and prilocaine cream (eg, EMLA, Lidopril) or oral sucrose solution on a pacifier also reduces pain and associated stress but to a lesser extent than local anesthesia. Studies have shown that blocks seem to be more effective than topical cream or oral sucrose, and the ring block is better than the dorsal penile nerve block. Infants who receive block anesthesia cry less and have less tachycardia and irritability in addition to fewer behavior changes during the 24 hours after the procedure. For older, prepubertal children who require formal surgical excision, sutureless circumcision using tissue glues has been associated with reduced surgical time and improved cosmetic outcome.

Post-Procedure Care

Oral acetaminophen can be administered for apparent pain or irritability. Analgesia is rarely needed after 24 hours. The parent or caregiver should be advised to watch for and report any bleeding or signs of infection. Mild redness and a yellowish crust may persist for 1 week. To keep the glans from sticking to the diaper, the parent or caregiver should apply a smear of petrolatum to the front of the diaper for 1 week.

Complications

Several complications are associated with circumcision in newborns (Box 27.1). The most common complication is bleeding, which may occur in 0.2% to 8% of patients. Typically, bleeding can be controlled using local pressure. More significant bleeding may require local pressure with 1:1,000 adrenaline-soaked gauze or with the use of other topical agents (eg, Surgicel, QuikClot). The second most common complication is infection, which is reported in up to 8% of circumcised newborns. The Plastibell device is associated with a higher incidence of infection than the Gomco clamp. Local treatment is sufficient to manage most infections, although intravenous antibiotics should be considered because neonatal sepsis and necrotizing fasciitis may occur secondary to infection following circumcision.

Poor cosmetic outcome is another complication of circumcision. Phimosis may occur if removal of the foreskin is insufficient. Inadequate freeing of the foreskin from the inner preputial epithelium may result in a concealed penis, with the shaft retracted backward into the abdominal wall. Skin bridges may form between the glans and shaft, resulting in the accumulation of smegma or tethering of the erect penis. Most post-circumcision adhesions are reported to resolve at the time of puberty with the onset of masturbation or sexual activity.

In the immediate postoperative period, urinary retention may occur secondary to tight surgical bandages. This complication can be prevented by applying local pressure rather than tight bandages to obtain hemostasis. Meatitis and meatal ulcers, which may be the result of irritation from ammonia or damage to the frenulum artery at the time of circumcision, have been reported in circumcised males. Inclusion cysts that represent implantation of smegma also have been reported. Additional injuries following circumcision may include penile lymphedema, urethrocutaneous fistulae secondary to misplaced sutures, penile cyanosis, and necrosis secondary to a tight Plastibell device. Wound dehiscence, which involves separation of the penile skin from the mucous membrane and denudation of the penile shaft, may occur more frequently with the Gomco clamp than the Plastibell device.

Meatal stenosis appears as a pinhole urethra with an angulated or narrow urinary stream and may be associated with enuresis or incontinence. Meatal stenosis is very rare in uncircumcised males; it is not clear whether circumcision is the direct cause of this rare, possibly late complication. A chronic inflammatory process resulting from inadequate post-procedure care, the use of superabsorbent

disposable diapers, urinary ammonia, or diaper dermatitis may contribute to the development of meatal stenosis.

Prognosis

The prognosis after circumcision is excellent, and complications are exceedingly rare.

CASE RESOLUTION

The risks and benefits of circumcision should be discussed with the mother. The father should be encouraged to participate in the decision making process. If the parents elect to forgo circumcision for their son, they should be instructed on the appropriate care of the uncircumcised penis, which involves gentle external washing without retraction of the foreskin.

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CHAPTER 28

Nutritional Needs

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CASE STUDY

At a routine health maintenance visit, a mother asks if she may begin giving her 4-month-old daughter solid foods. The infant is taking about 4 to 5 oz of formula every 3 to 4 hours during the day (about 32 oz per day) and sleeps from midnight to 5:00 am without awaking for a feeding. Her birth weight was 3.2 kg (7 lb), and her present weight and length (5.9 kg [13 lb] and 63.5 cm [25 in], respectively) are at the 50th percentile for age. The physical examination, including developmental assessment, is within reference limits.

Questions

1. What are some of the parameters that may be used to decide when infants are ready to begin taking solid foods?
2. Up to what age is human milk or infant formula alone considered adequate intake for infants?
3. At what age do infants double their birth weight? At what age do they triple their birth weight?
4. What allergy risks are associated with the early introduction of solid foods?

Good nutrition is essential for typical growth and development. The physician plays an important role not only in assessing the growth of children but also in counseling parents about the nutritional needs of maturing children. The primary care physician should be knowledgeable about key nutritional concepts for children, including typical growth patterns and assessment of the child's nutritional status, changing nutritional requirements and feeding patterns from infancy through adolescence, and common feeding and nutritional disorders.

Growth Patterns and Nutritional Requirements of Typical Children

Monitoring the growth and nutritional status of infants and children is an integral component of well-child care. The average expected increases in weight, height, and head circumference for the first several years after birth are listed in Table 28.1.

The energy and nutritional requirements of children vary with age. Postnatal growth is most rapid during the first 6 to 12 months after birth; hence, caloric and protein needs are very high at this time. The average daily energy and protein needs of children from birth to 18 years of age are presented in Table 28.2.

On average, newborns weigh 3.5 kg (7.7 lb), are about 50 cm (20 in) long, and have a head circumference of 35 cm (14 in). They lose about 5% to 10% of their birth weight during the first several postnatal days and usually regain this weight by the age of 10 to 14 days. During the first several months after birth, weight gain serves as an important indicator of infants' general well-being. Failure to gain weight during this time may be a clue to a wide variety of problems, ranging from underfeeding to malabsorption. Newborns and infants gain about 30 g/day (1.1 oz/day; roughly 1% of their birth weight per day) for the first 3 postnatal months and about 10 to 20 g/day (0.4–0.7 oz/day) for the rest of the first year. Infants double their birth weight by 6 months of age and triple their birth weight by 12 months of age. Children aged 2 years to puberty gain approximately 5 to 10 g/day (0.2–0.4 oz/day). On average, children weigh about 10 kg (22 lb) at 1 year of age, 20 kg (44 lb) at 5 years of age, and 30 kg (66 lb) at 10 years of age. A rough rule that can be used to estimate the expected weight of a child based on age is 2 × age (years) + 10 = weight (kg). A prepubertal child who does not gain at least 1 kg/year should be monitored for nutritional deficits.

Infants and young children grow about 25 cm (9.8 in) during the first postnatal year, 12.5 cm (4.9 in) during the second year, and 6.25 cm (2.5 in) per year after that until puberty. This is followed by the prepubertal-pubertal growth spurt. Girls grow 3 to 4 cm (1.2–1.6 in) every 6 months and boys grow 5 to 6 cm (2.0–2.4 in) every 6 months during this period.

Feeding Patterns of Infants and Children

Liquid Foods

Human milk is generally recommended as the exclusive nutrient for newborns and infants during the first 6 months after birth and then could be continued along with complementary foods through 12 months of age. However, there are situations in which breastfeeding is not possible for the mother or is contraindicated because of a disease or medication. Therefore, although breastfeeding is the most advantageous for mother and baby and should be encouraged, mothers should never be made to feel inadequate or guilty if they are unable to breastfeed. Human milk or an iron-fortified infant formula provides complete nutrition for infants during the first 4 to 6 months after birth. During the first postnatal month or 2, newborns and infants take about 2 to 3 oz of formula (approximately 10 minutes on each breast) every 2 to 3 hours.

Table 28.1. Expected Increase in Weight, Height, and Head Circumference of Newborns, Infants, and Children

Typical Weight Gain	
Age	*Expected Weight Increase*
0–3 months	25–35 g/day (0.9–1.2 oz/day)
3–6 months	12–21 g/day (0.4–0.7 oz/day)
6–12 months	10–13 g/day (0.4–0.5 oz/day)
1–6 years	5–8 g/day (0.2–0.3 oz/day)
7–10 years	5–11 g/day (0.2–0.4 oz/day)
Typical Height Increase	
Age	*Expected Height Increase*
0–12 months	25 cm/year (9.8 in/year)
13–24 months	12.5 cm/year (4.9 in/year)
2 years–puberty	6.25 cm/year (2.5 in/year)
Typical Increase in Head Circumference	
Age	*Expected Increase in Head Circumference*
0–3 months	2 cm/month (0.8 in/month)
4–6 months	1 cm/month (0.4 in/month)
7–12 months	0.5 cm/month (0.2 in/month)
Total increase	12 cm year (4.7 in) in first year

Table 28. 2. Energy and Protein Needs of Children

Age (years)	*Calories (kcal/kg/day)*	*Protein (g/kg/day)*
0–1	90–120	2.5–3.0
1–7	75–90	1.5–2.5
7–12	60–75	1.5–2.5
12–18	30–60	1.0–1.5

Because human milk is more easily digested than formula, it passes out of the stomach in 90 minutes; formula may take up to 4 hours. Therefore, during the first 4 to 6 postnatal weeks, breastfed newborns and infants want to feed more frequently (8–12 times in 24 hours) than formula-fed newborns and infants (6–8 times in 24 hours), with an increased number of nighttime feedings as well. By about 3 to 5 months of age, breastfed and bottle-fed infants do not differ in the number of nighttime feedings, although some breastfed infants continue to wake out of habit.

Most infants 6 months or younger consume about 4 to 5 oz per feeding every 4 to 5 hours. Under routine circumstances, human milk is preferred to infant formulas because it has emotional, nutritional, and immunologic advantages. Breastfeeding allows infants and mothers to develop a unique relationship that can be emotionally satisfying (see Chapter 29).

The composition of human milk varies over time. Colostrum, the first milk produced after delivery, is high in protein, immunoglobulin (Ig), and secretory IgA. Colostrum gradually changes to mature milk 7 to 10 days after delivery. The nutrient content of human milk of mothers who deliver preterm compared with those who deliver at term may vary considerably. Individual assessment may be necessary to determine the appropriateness of human milk for preterm newborns.

Nutritionally, human milk is uniquely tailored to meet the specific needs of babies. Human milk provides approximately 20 kcal/oz, the same as routine infant formulas. Table 28.3 compares the composition of human milk and several infant formulas. Human milk has relatively low amounts of protein compared with cow's milk (1% vs 3%), yet the levels are sufficient to provide for satisfactory growth of babies. Protein content is highest at birth at 2.3 g/dL, then declines over the first month to 1.8 g/dL, yet it ensures adequate protein status throughout the first postnatal year.

Qualitative differences also make human milk more desirable. Casein to whey ratio in human milk is about 30:70, making it easier to digest than most infant formulas, which tend to have higher casein to whey ratios at 82:18. Whey is more easily digested and associated with faster gastric emptying compared with casein. Newborns and infants who breastfeed tend to digest their milk more easily, have softer stools, and be less satiated overnight, requiring more feeds, than those fed formula. Other whey proteins, such as IgA, lysozyme, and lactoferrin, all contribute and help host defenses.

Lactose is the major carbohydrate of human and cow's milk, but it is present in higher concentrations in human milk. Lactose in human milk also contributes to softer stool consistency with nonpathological fecal flora and improved absorption of minerals. Oligosaccharides in human milk found in the carbohydrate polymers and glycoproteins have been structurally shown to mimic bacterial antigen receptors and may have a role in host defense. Fat is the primary source (50%) of calories in human milk. The fat in cow's milk, which contains primarily saturated fatty acids, is not as well digested by newborns and infants as human milk fat, which is predominantly composed of polyunsaturated fats. Within the last decade, the long-chain polyunsaturated fatty acids docosahexaenoic acid (DHA) and arachidonic acid (ARA) have been added to most infant formulas to simulate the higher levels found in human milk. Research continues to be inconclusive, however, as to whether DHA and ARA supplementation may enhance vision and improve growth and cognitive development in formula-fed infants.

Human milk from well-nourished women should provide adequate amounts of all vitamins and other micronutrients. However, vitamin K, vitamin D, iron, and fluoride are not present in sufficient quantities to satisfy all nutritional needs over a prolonged period, and supplementation should be considered. The American Academy of Pediatrics (AAP) recommends that all newborns receive a prophylactic dose of 0.5 to 1 mg of parenteral vitamin K in the immediate newborn period to help prevent bleeding disorders. Even though the vitamin D content of human milk is low compared with cow's milk, newborns and infants of healthy mothers have generally not been observed to develop rickets if

Table 28.3. Composition of Human Milk and Select Infant Formulas (Calories: 20 kcal/oz)

Formula	*Protein*	*Carbohydrate*	*Fat*
Human milk (mature)	40% casein and 60% whey	Lactose	Human milk fat
Cow's milk	80% casein and 20% whey	Lactose	Butterfat
Enfamil NeuroPro	Nonfat cow's milk and whey	Lactose	Palm olein, soy, coconut, and high-oleic sunflower oils; DHA, milk fat globule membrane
Similac Advance	Nonfat cow's milk and whey	Lactose	High-oleic safflower oil, coconut and soy oils, DHA
Enfamil ProSobee	Soy protein and methionine	Corn syrup solids	Palm olein, soy, coconut, and high-oleic sunflower oils
Similac Soy Isomil	Soy protein and methionine	Corn syrup solids and sucrose	High-oleic safflower oil, soy and coconut oils; DHA
Nutramigen with DHA & ARA	Casein hydrolysate, cystine, tyrosine, tryptophan	Corn syrup solids and cornstarch	Palm olein, soy, coconut, and high-oleic sunflower oils; DHA, ARA
Pregestimil with DHA & ARA	Casein hydrolysate, cystine, tyrosine, tryptophan	Corn syrup solids, modified cornstarch, and dextrose	MCT, high-oleic safflower, corn and high oleic vegetable oils, DHA, ARA
Similac Expert Care Alimentum	Casein hydrolysate, cystine, tyrosine, tryptophan	Sucrose modified tapioca starch	Safflower oil, MCT, soy oil, DHA, ARA

Abbreviations: ARA, arachidonic acid; DHA, docosahexaenoic acid; MCT, medium-chain triglycerides.

there is sufficient exposure to sunlight. Newborns require about 1 minute of exposure to sunlight on the face to produce enough vitamin D. However, adequate sun exposure is difficult to assess, and there are increasing concerns about the harmful effects of sunlight. Compared with the previous recommendation of an average intake of 200 IU of vitamin D per day, the 2010 Institute of Medicine, now known as the Health and Medicine Division of the National Academies, recommendation calls for an average intake of 400 IU of vitamin D per day to meet the needs of most infants younger than 12 months. Although human milk contains less iron than iron-fortified formulas (fortified to about 12 mg/L of iron), the bioavailability of the iron in human milk is greater. Breastfed infants do not need iron supplementation until 6 months of age. For children 6 months and older who live in communities with suboptimally fluoridated water, the AAP recommends systemic (dietary) supplementation. Such supplementation can be provided through the use of a fluoridated toothpaste twice a day (see Chapter 31).

Human milk has several immunologic advantages, which are allergy and infection protective, over standard cow's milk–based formulas. Its allergy-protective characteristics are attributed, in part, to the decreased intestinal permeability associated with human milk compared with standard formulas. The host defense factors present in human milk include Ig, complement, and cellular components (eg, macrophages, neutrophils, lymphocytes). Studies have shown that the incidences of viral and bacterial illnesses are lower in exclusively breastfed infants compared with their formula-fed peers.

The AAP recommends exclusive breastfeeding for about 6 months, followed by continued breastfeeding as complementary foods are introduced, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant. Rarely, breastfeeding is contraindicated (see Chapter 29).

Solid Foods

Supplemental foods may be added to infants' diets between the ages of 4 and 6 months. Solid foods should be introduced as soon as infants require the additional calories and are developmentally mature (ie, infant can sit and support his or her head and has lost tongue thrust). Introduction of solid foods prior to 4 months of age can interfere with an infant's ability to take sufficient amounts of human milk or formula to meet nutritional needs. Waiting beyond 6 months of age to introduce solid foods may increase an infant's risk of having inadequate iron or zinc intake.

Infants should first be given cereal grains, fruits, and vegetables, although 2 to 3 days should separate the introduction of new foods. Once several of these foods have been tolerated, the early introduction of subsequent, more allergenic, foods, such as milk, eggs, soy, wheat, nuts, and seafood, between 4 and 6 months of age may decrease the risk of the infant developing food allergies. Factors that indicate infants may be ready for solid foods include current weight twice that of birth weight, or about 6 to 7 kg (13.2–15.4 lb); consumption of more than 32 oz of formula per day (if on a formula-only diet); frequent feeding (regularly more than 8–10 times per day or more often than every 3 hours); and perceived persistent hunger after nursing.

Iron-fortified infant cereal, most commonly rice cereal because it does not contain gluten, is usually the first solid food offered to infants. Other single-grain cereals, such as barley cereal or oatmeal, are also appropriate early supplemental foods. Precooked infant cereals can be mixed with a variety of liquids, including human milk, formula, water, or infant fruit juices. The vitamin C in juice increases the bioavailability of the iron in the cereal, hence the

recommendation to add it to dry cereal. Initially, the cereal should be mixed to a thinner consistency (eg, about 1 tablespoon of cereal to 2 oz of liquid). It is not unusual for infants to reject their first several spoonfuls of cereal because the tastes and textures are new. If they refuse the feeding, it should be stopped and reintroduction of the food delayed for 1 week. Once infants have accepted the new taste and texture, the mixture should gradually be worked to a thicker consistency. By about 7 to 8 months of age, infants should be taking 4 to 6 tablespoons of cereal mixed with enough liquid to give the mixture the consistency of mustard. Mixed cereal grains may be given to older infants.

Fruits and vegetables may be introduced within a few weeks of the introduction of cereal. The order is not as important as the need to add only 1 new food at a time and no more than 1 to 2 new foods per week. Meats may be introduced after 6 months of age.

A wide variety of commercially prepared baby foods designed to be developmentally appropriate and labeled by stage (ie, first, second, third) are available. The jars of different stages contain the amount of food that an infant at a given age should be able to eat at 1 sitting. This is not always the case, however, and opened jars of baby food may safely be stored in the refrigerator for 2 to 3 days. Infants should not be fed directly from the jar because saliva on the spoon mixes with the remaining food and digests it, causing it to liquefy. Vegetables and meats may be offered at room temperature but should be warmed slightly for greater palatability. Fruits and desserts may be at room or refrigerator temperature. Home-cooked fruits and vegetables should be thoroughly washed, pureed, and strained before giving to infants. Home-prepared foods tend to have a shorter shelf life than commercially bought baby foods because of lack of preservatives, but some may find that they are more palatable to the infant.

First-stage foods, for infants 4 to 6 months of age, include strained infant juices, single-grain cereals, and pureed strained fruits and vegetables such as bananas, carrots, and peas. These foods contain no egg, milk, wheat, or citrus, to which some infants may be sensitive. Second-stage foods, for infants about 6 to 9 months of age, are smooth, mixed-ingredient foods, such as mixed vegetables, or meat dinners, such as chicken noodle. Third-stage foods, or junior foods, are for infants about 9 to 10 months of age who can sit well without support, have some teeth, and have begun self-feeding. These more coarsely textured foods, such as vegetable and meat dinner combinations, contain a wider variety of nutrients. Finger foods, such as crackers, cheese wedges, or cookies, can also be introduced by 9 to 10 months of age, once infants have developed a pincer grasp. Most infants are eating the same meals as the rest of the family (table foods) by about 1 year of age. Foods that can easily be aspirated, such as raw carrots, nuts, and hard candies, should be avoided until children are older than 4 years.

Baby foods can be prepared at home as long as they are finely pureed or strained and contain enough liquid to make them easy for infants to swallow. One danger of preparing foods at home is that sugar, salt, or spices can be easily added to make foods palatable to adults. These ingredients are not necessary for infants. In addition, homegrown, home-prepared vegetables may be contaminated with high levels of nitrates (eg, because of contaminated well water) and nitrites (eg, in vegetables such as carrots, beets, and spinach). Nitrates and nitrites have been implicated in the development of methemoglobinemia, especially in infants younger than 6 months. Methemoglobinemia decreases the oxygen-carrying capacity of the blood, leading to anoxic injury and death. This is more of a concern in rural areas that primarily use well water.

Weaning from the breast or bottle to a cup usually occurs by 12 months of age but may be delayed up to 18 months of age in some children. Homogenized, vitamin D–fortified cow's milk may be given at 12 months of age. Fat-free (skim) and low-fat (1%) milk should not be given before 2 years of age.

Diet of Children and Adolescents

The caloric and protein needs of children decrease in the second year after birth, paralleling the decrease in growth rate during this time. Milk intake also decreases and may drop to 16 oz/day by 24 to 36 months of age. Except for increased caloric requirements, the diet of school-age children and adolescents should be similar to that of normal adults. Evidence that foods eaten during childhood may have long-lasting effects on adult health is increasing, and it is important that children develop healthy eating habits early in life. Atherosclerosis, osteoporosis, and obesity are some of the diseases that may have their beginnings during childhood.

The US departments of Agriculture (USDA) and Health and Human Services (HHS) have replaced the food pyramid with a new visual aid—a circular plate on a square mat. Half of the plate consists entirely of vegetables and fruits, whereas the other half of the plate is divided into one-quarter protein and one-quarter grains, with a small side of dairy. It's a much more visually descriptive tool that guides how to divide daily meals. The website www.choosemyplate.gov provides individual dietary guidance according to a child's age, sex, and activity level based on the USDA/HHS dietary guideline for Americans older than 2 years.

To promote lifelong heart healthy habits, the American Heart Association (AHA) released a statement of dietary recommendations for children and adolescents (Box 28.1). It recognizes that children are often offered nutrient-poor foods that are high in fat and sugar and overly processed. The AHA recommendations support USDA

Box 28.1. AHA Dietary Recommendations for Children and Adolescents

- Limit total fats to less than 25% to 35% of total daily calories.
- Limit saturated fat to less than 7% of total daily calories.
- Limit trans fat to less than 1% of daily calories.
- Remaining fat should come from natural sources of monounsaturated and polyunsaturated fats, such as unsalted nuts and seeds, fish (especially oily fish, such as salmon, trout, and herring, at least 2 times a week), and vegetable oils, such as canola oil.
- Limit cholesterol intake to less than 300 mg a day or, if you have coronary artery disease, less than 200 mg a day.

guidelines and include eating fruits and vegetables daily while limiting fruit juice intake, using vegetable oils, using butter instead of soft margarines, eating whole grain rather than refined grain breads and cereals, using nonfat or low-fat milk and dairy products, eating more fish, and reducing salt intake.

The AHA also encourages behaviors for parents and caregivers that promote healthy habits for the whole family. These recommendations ask parents and caregivers to choose mealtimes, provide a social context for eating by having regular family meals, lead by example in their own eating habits, and allow children to self-regulate food intake and not to force them to finish meals if they are not hungry.

Children who consume a varied diet do not need routine vitamin supplementation. However, children and teenagers who are considered picky eaters, as well as children at nutritional risk, may benefit from supplementation. This includes children and teenagers who are anorexic or those who follow fad diets, those with chronic diseases, those who consume a vegetarian diet, and those with failure to thrive (FTT). A standard pediatric vitamin-mineral supplement should contain no more than the dietary reference intakes of its components. Parents should be counseled to teach their children that supplements are not candy and to keep them out of reach. Serious overdoses can occur, especially with iron-containing formulations.

Bone health is determined by calcium and vitamin D intake as well as weight-bearing physical activity. Recent data suggest the possibility of other important health benefits throughout life of these key nutrients and behavior, in addition to bone growth and development. The 2010 Institute of Medicine guidelines call for a recommended daily allowance of 600 IU per day of vitamin D for children older than 1 year and 1,300 mg of calcium per day for children and adolescents 9 to 18 years of age. Unfortunately, calcium intake for most US children, particularly adolescents, is generally below the recommended levels. Barriers to adequate calcium intake may be due to the preference of sweetened juice and soft drinks over milk as well as lactose intolerance in certain populations. Nondairy calcium sources include salmon, white beans, broccoli, and calcium-fortified foods, such as orange juice, breakfast cereals, and soy milk. Adequate calcium intake can be achieved by eating 3 (or 4 for adolescents) age-appropriate servings of dairy products or other calcium-rich food per day. In children and adolescents who do not consume adequate amounts of calcium from dietary sources, a calcium supplement is recommended. This can be in the form of a multivitamin in the younger child or calcium carbonate tablets with or without vitamin D for the adolescent.

Adolescence is a period of tremendous physical and emotional growth, both of which greatly affect nutritional needs and habits. Although their rapid physical growth requires increased energy and nutrients, the common eating habits of teenagers do not always support their needs. Teenagers tend to skip meals, eat outside the home, consume fast food and snacks, and experiment with different restrictive fad diets or various forms of vegetarianism.

Teenage athletes also have their own unique nutritional concerns. They want to maximize performance while maintaining the desired physique for their particular sport or weight class. While there are many nutritional supplements, such as creatinine, carnitine, various amino acids, and dehydroepiandrosterone, that claim to enhance athletic performance, none has thus far been fully evaluated scientifically. Instead, teenage athletes should be counseled on the importance of a basic nutrient: water. Proper hydration does enhance performance and prevents heat injury. Approximately 4 to 8 oz of fluid for every 15 minutes of exercise is recommended regardless of actual thirst. Carbohydrate loading before competition is believed to enhance performance; however, this practice has no effects on non-endurance events and may confer only a modest effect for endurance events by prolonging time to exhaustion. In counseling a teenage athlete, specific questions should also be directed to elicit any unhealthy practices to maintain or lose weight.

Vegetarianism is gaining popularity among adolescents. Reasons for choosing vegetarianism are varied, including health benefits, means for weight loss, animal cruelty concerns, and religious beliefs. It is important to ask vegetarians about their specific restrictions, as these relate to their nutritional risks. Semi-vegetarians are those who avoid red meat but eat fish and chicken in moderation. Lacto-ovo vegetarians consume animal products, such as dairy and eggs, but avoid animal flesh. Vegans do not eat any animal products, such as dairy, eggs, honey, or gelatin. Those who follow a macrobiotic diet restrict not only animal products but also refined and processed foods, foods with preservatives, and foods that contain caffeine or other stimulants.

A well-planned vegetarian diet can provide all necessary nutrients; however, many teenagers experiment with vegetarianism in a non-vegetarian household and require guidance. The nutrients that may be deficient in a vegetarian diet are protein, calcium, vitamin D, vitamin B_{12}, iron, and zinc. Protein intake is usually not a concern for lacto-ovo vegetarians because eggs and dairy have high-quality proteins. Vegans and macrobiotic followers have a variety of plant-based protein sources from which to choose, such as legumes, cereals, nuts, seeds, and fruits. Because vitamin B_{12} is only found in animal-based foods, vegans and macrobiotic followers must ensure adequate intake via supplements or by consuming vitamin B_{12}-fortified foods, such as soy and nut beverages and cereals.

Lastly, familiarity with the latest fad diets is an asset for any primary care practitioner. These diets are usually restrictive in certain nutrients and recommend unusual dietary patterns that are inconsistent with current USDA guidelines. Although there are some suggestions that these diets work for some adults, there are almost no scientific data for children and adolescents. To keep abreast of the latest fads, refer to the Academy of Nutrition and Dietetics (www.eatright.org), which maintains an annual review of such popular fad diets.

Evaluation

History

Nutritional assessment begins with a complete dietary history. The dietary assessment should emphasize the quantity, quality, and variety of foods in the diet. Any special or restricted dietary habits

should be noted (eg, vegetarian diet, vegan diet, occasional vegetable juicing/fasting). A 3-day food record listing the types and quantities of food eaten throughout the day can be very helpful in evaluating dietary history.

In addition, the child's routine medical, family, and social history all may influence nutritional status. For example, the economic status of families may affect the variety and type of foods they may be able to purchase, and the level of education of parents influences their ability to understand the concepts of a healthy diet. Poverty and ignorance of nutritional needs are among the most common reasons for malnutrition in children. It is vital that the pediatrician stress to families the value of healthy food choices at each physical examination. Family access to food can be estimated by asking parents about how often the family skips meals during the average month. Such information assesses food insecurity within a household. Specific cultural food preferences and feeding practices should also be included in the history.

Physical Examination

Weight, length or height, head circumference, weight for length, and body mass index should be measured or calculated routinely and plotted on a longitudinal basis on appropriate growth curves. In addition to the charts provided by the Centers for Disease Control and Prevention and World Health Organization, additional charts are available for special populations for which growth is altered, such as infants and children with low birth weight and preterm birth, Down syndrome, Turner syndrome, Williams syndrome, and several other chromosomal and genetic disorders. Changes in the rate of growth over time are more useful than a single measurement in the assessment of nutritional problems. Calculation of the height age (age for which the child's height is at the 50th percentile), weight age (age for which the child's weight is at the 50th percentile), and ideal weight for actual height may be useful when deviations from reference are noted.

In addition to the overall impression of nutritional status, certain findings on physical examination may be characteristic of particular nutritional disorders. The evaluation of the hair, skin, eyes, lips and oral mucosa, dentition, and musculoskeletal system should be emphasized because the examination of these areas is most likely to show the effects of malnutrition. Muscle wasting; hepatosplenomegaly; skeletal deformities; decayed teeth; rough, dry skin; hair that is easily plucked; and irritability may all be signs of inadequate nutrition.

Laboratory Tests

Suspected malnutrition or nutrition-related disorders, based on history and physical examination, can be further investigated with laboratory studies. Tests that may be used in the evaluation of anemia, 1 of the most common nutrition-related disorders seen in children, include a complete blood cell count, reticulocyte count, serum iron, ferritin, and total iron-binding capacity. Investigation of suspected malnutrition begins with an assessment of protein status, with measures of indicators such as serum albumin, total protein, and transthyretin. Liver function tests and a lipid profile may also be useful in the evaluation of suspected malnutrition. Screening tests that may be used in the evaluation of FTT include thyroid function studies, urinalysis, and bone age (see Chapter 146). More specific tests, such as serum vitamin levels (eg, folate or vitamin B_{12} levels in suspected malabsorption) or hormone assays (eg, growth hormone levels in the evaluation of short stature), may be obtained in certain instances.

Common Feeding and Nutritional Problems of Childhood

Several gastrointestinal (GI) problems have been attributed to diet. A small amount of spitting up is seen in most children, especially during the first 6 months after birth. However, vomiting can be a sign of several disorders, ranging from viral GI tract infections to more severe illnesses, such as pyloric stenosis, urinary tract infection, GI obstruction, or inborn error of metabolism (see Chapter 120). Constipation, which is seen more commonly in formula-fed than breastfed infants, may be due to insufficient fluid intake (see Chapter 124). The simple addition of 2 to 4 oz of water to an infant's diet or temporary use of diluted apple or prune juice may solve the problem.

Chronic nonspecific diarrhea of childhood, or "toddler's diarrhea," may be seen in infants and children 6 months to 5 years of age with low dietary fat intake and excessive fruit juice consumption (see Chapter 123). Failure to absorb sugars, especially sorbitol and fructose, can lead to an osmotic diarrhea.

Underfeeding or a diet that is not nutritionally balanced may result in FTT (see Chapter 146). The opposite problem, obesity, is among the most common nutritional problems of children in the United States (see Chapter 155). The prevalence of this condition in children 6 to 11 years of age is estimated to be about 20% to 25%. Finally, the eating disorders anorexia nervosa and bulimia nervosa are estimated to affect about 1 in 100 adolescent females 16 to 18 years of age (see Chapter 64).

The picky eater is a common parental concern in the primary care setting. For practitioners who work with the Latinx population, the child who "no come nada," literally translated as the child who "does not eat anything," is a similar common parental concern. Parents can be reassured by their child's normal weight for height or body mass index and growth velocity. They should be counseled that it is normal for preschoolers to exert their individuality by limiting food preferences, the fact that it may take up to 10 exposures for a child to accept a new food, the difference between child and adult portion sizes, and the concept that children can self-regulate food intake to sustain normal growth and health.

Nutritional disorders include malnutrition and deficiencies of vitamins and minerals. Iron deficiency anemia is 1 of the most common nutrition-related problems seen in children and adolescents. Malnutrition is among the leading causes of childhood morbidity and mortality worldwide. Although primary protein-calorie malnutrition (PCM) is rare in most parts of the United States, surveys conducted on pediatric wards have demonstrated that about one-third of pediatric inpatients with chronic disease have evidence of

some degree of PCM. The most common deficits were weight for height below 90% of standard (ie, evidence of acute malnutrition) and height for age below 95% of standard (ie, evidence of chronic malnutrition). The 2 forms of PCM are marasmus (severe caloric depletion) and kwashiorkor (inadequate protein intake). Untreated PCM can result in impaired growth, poor intellectual development, and impaired immune functioning.

CASE RESOLUTION

The infant is ready to begin some solid foods because she is consuming 32 oz of formula per day and continues to be hungry. In addition, she has reached a weight of 5.9 kg (13 lb) and has almost doubled her birth weight. The mother is counseled to begin feeding her daughter a single-grain infant cereal mixed with formula. (The cereal should be fed by spoon, not given in a bottle.) Within a few weeks, once the infant is taking the cereal well, other first foods, such as fruits and vegetables, may be introduced. After she tolerates cereal and several fruits and vegetables, more allergenic foods, such as egg or diluted nut butters, should be introduced in small amounts to reduce the risk that she will develop a subsequent food allergy.

Resources

ChooseMyPlate.gov
www.choosemyplate.gov
US Department of Agriculture National Agricultural Library Food and Nutrition Information Center: https://www.nal.usda.gov/fnic

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CHAPTER 29

Breastfeeding

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CASE STUDY

A 25-year-old pregnant woman comes to your office with her 18-month-old for a well visit. When asked, she reports that she had a difficult time breastfeeding her first child because of pain; however, she gave pumped milk for 4 months. She hopes to breastfeed directly for at least 6 months with this baby. She would like to know what advice you can give her. She expects a normal delivery, has had no breast surgery, and is not on any medications; however, she smokes cigarettes occasionally. She plans to return to work when the baby is 4 months old.

Questions

1. What is the normal physiology of lactation?
2. What are the benefits of breastfeeding?
3. What are the contraindications to breastfeeding?
4. What management maximizes a mother's success at breastfeeding?
5. How does the pediatrician manage some of the common problems that may arise during breastfeeding?

Human milk is the natural food source for human newborns and infants. It provides optimal nutrition and is an immunologically active compound that allows for early regulation of an infant's immune system and priming of the microbiome. All formulas are incomplete attempts at replication. Human milk is made of water, fat, lactose-containing carbohydrates, and protein, as well as vitamins, immunoglobulins, prebiotics, enzymes, hormones, and even phagocytes and lymphocytes. It is a dynamic fluid that changes in composition as newborns and infants grow. Early colostrum is high in lactose and protein, composed of casein and whey, and quite immunologically active. Through lactogenesis, it becomes mature milk with much greater quantity and higher fat content. It thus has a lower concentration of protein but continues to contain all the immunologically active components of colostrum.

Epidemiology

Historically, newborns and infants were totally dependent on breastfeeding by their mother or a wet nurse for their survival. When formula feeding was attempted in the 1800s, the mortality rate in exposed newborns and infants was as high as 85%. Thus, the advantages of breastfeeding were recognized and still promoted in the early 1900s. Following the advent of pasteurization, cow's milk formula became much safer than before pasteurization. Formula development allowed more mothers to enter the workforce, and breastfeeding rates declined over the course of the 20th century. Formula feeding became the norm as companies successfully marketed formulas. In 1972, at the nadir of breastfeeding, only 22% of babies were ever breastfed. However, current scientific understanding of the many benefits of breastfeeding for baby and mother has been the impetus to again promote breastfeeding as the preferred food source for newborns and infants.

In the United States today, following the Centers for Disease Control and Prevention Healthy People initiative, which included a national agenda calling for an increased rate of breastfeeding, 83.2% of mothers are initiating breastfeeding. The rate of mothers sustaining breastfeeding to 1 year of age is only 35.9%, however. Rates are lower in low socioeconomic groups and among women with lower levels of education. Ethnic disparities also exist, with the black population having the lowest rates of breastfeeding in the United States.

In 1991, the World Health Organization and the United Nations Children's Fund developed the Baby-Friendly Hospital Initiative, delineating 10 steps to undertake in the hospital to promote successful breastfeeding. This initiative is used worldwide to improve breastfeeding rates. The American Academy of Pediatrics published its policy statement, "Breastfeeding and the Use of Human Milk," in 2005 and a revised version in 2012. This policy endorses breastfeeding and delineates the physician responsibility to promote and support it. In 2011, the US Department of Health and Human Services issued *The Surgeon General's Call to Action to Support Breastfeeding.* A national imperative now exists to promote breastfeeding.

Anatomy and Physiology of Lactation

The breasts consist of lobules and alveoli where milk is produced, as well as the ductile system, leading to 9 to 15 milk duct openings in the nipple. During pregnancy, the breasts enlarge as lobules mature and differentiate in response to estrogen, placental lactogen, prolactin, and progesterone. The nipples darken, and the surrounding areolas enlarge. In the first 24 hours after delivery, only a small

volume of colostrum, approximately 40 to 50 mL total, is produced. By 3 to 4 days after delivery, however, increased milk production, termed *lactogenesis stage 2,* commences. This occurs as estrogen and progesterone levels drop and prolactin, from the anterior pituitary, is increased in response to nipple stimulation. Additionally, oxytocin is released from the posterior pituitary and causes contraction of myoepithelial cells, which squeeze milk from the alveoli. Although initial production of milk is not dependent on newborn suckling, the more the neonate feeds and the more often the breast is effectively emptied, the more milk is produced. If milk is not removed, an autocrine hormone in milk called feedback inhibitor of lactation acts locally within each breast to inhibit milk production. Early effective removal of colostrum, ideally starting within 1 hour of delivery, speeds the arrival of increased milk volume, and frequent milk removal increases supply in the weeks that follow.

Benefits of Breastfeeding

For the baby, the benefits of breastfeeding are myriad. Studies have demonstrated that breastfed infants have a decreased incidence and severity of infectious illnesses, including diarrhea, respiratory infections, otitis media, bacterial meningitis, and urinary tract infections. They have lower rates of hospitalization and mortality. The incidence of otitis media is 100% higher in formula-fed infants than exclusively breastfed infants. Studies have also demonstrated better performance on cognitive testing among children who were breastfed as infants. Among preterm infants fed human milk, the incidence of necrotizing enterocolitis is also significantly reduced. Breastfeeding in infancy also reduces the later incidence of atopy, allergies, asthma, childhood obesity, type 2 diabetes, and even childhood cancer. Decreased rates of sudden infant death syndrome (see Chapter 72) have also been documented. All these benefits are increased by increasing the length and exclusivity of breastfeeding.

For the mother, an immediate benefit to breastfeeding is oxytocin-induced decreased postpartum blood loss and enhanced mother-infant bonding. Lactation amenorrhea may serve subsequently as birth control. Breastfeeding has also been associated with quicker return to prepregnancy weight as well as decreased risk of breast cancer, ovarian cancer, diabetes, hypertension, heart disease, and osteoporosis. Some evidence suggests that breastfeeding decreases the risk of postpartum depression.

Societal benefits from breastfeeding include markedly decreased annual health care costs. An estimated savings of $10.5 billion annually could be generated if 80% of American families breastfed exclusively for the first 6 months after birth.

Barriers to Breastfeeding

Many studies have evaluated barriers to breastfeeding in the United States. Understanding these barriers is essential to improving breastfeeding rates. With effective physician, nursing, and peer support, most mothers should be able to breastfeed successfully. One of the most important barriers is the lack of knowledge of pregnant women about the benefits of feeding mother's milk. Education beginning at the first prenatal visit is vitally important.

Some mothers report feeling uncomfortable breastfeeding in public. Identifying this issue and helping these mothers feel more supported or find privacy when they need it can help them succeed with breastfeeding. Currently, laws exist in all 50 states and the District of Columbia that protect a mother's right to breastfeed in public.

Many new mothers have poor family support for breastfeeding, and it is necessary to include the entire family in breastfeeding counseling. The mother will not be successful if her family is encouraging her to use formula.

Some mothers find that their place of employment does not make accommodations for a breastfeeding mother. It may be that the workplace needs to be reminded of laws promoting breastfeeding in the workplace. The Patient Protection and Affordable Care Act includes a provision that the workplace must provide adequate break time and a private place for nursing mothers to pump for up to 1 year. Some states offer additional protections.

Hospitals may have practices or policies that interfere with successful breastfeeding, including high rates of cesarean section or no rooming-in policy. Physicians should work with their hospitals to minimize these potential barriers. Some medical professionals become barriers to exclusive breastfeeding because they lack the knowledge to properly manage problems as they arise.

Contraindications

Absolute contraindications to breastfeeding are few. The neonate with galactosemia type I as detected by newborn screening and who therefore is unable to metabolize lactose or galactose may not exclusively breastfeed. Newborns can also inherit defects in protein metabolism that may necessitate a special diet, precluding breastfeeding. In most states, newborn screening now includes testing for most of these metabolic disorders.

Maternal infections prohibiting breastfeeding include active, untreated tuberculosis and HIV. Additionally, if herpetic vesicles are present on the breast, the mother should not breastfeed from that breast.

Medications and Drugs of Abuse

Most medications are safe for a mother to use while breastfeeding, and the risk to the newborn or infant of not breastfeeding often outweighs the risk of exposure to subclinical doses of the medication in human milk. Each medicine should be reviewed for potential effects on the infant or possible negative effects on milk supply. The LactMed App is an excellent free resource (https://toxnet.nlm.nih.gov/help/newtoxnet/lactmedapp.htm). Chemotherapeutic agents, antimetabolites, radioactive isotopes, and drugs of abuse are all contraindicated for breastfeeding. However, a mother with a history of drug use may benefit from breastfeeding provided her toxicology results are closely monitored and are negative.

The 2018 American Academy of Pediatrics clinical report on marijuana use during pregnancy and breastfeeding states that because the potential risks of infant exposure to marijuana metabolites are unknown, women should be informed of the potential risk of exposure during lactation and encouraged to abstain from using any marijuana products while breastfeeding. Although marijuana is legal in

some US states, pregnant and breastfeeding women who use marijuana may be subject to child welfare investigations if they have a positive marijuana screening result.

Breastfeeding Management

The management of breastfeeding should begin in the prenatal period. The US Preventive Services Task Force endorses promotion and support for breastfeeding at all health care encounters. The pregnant woman should be educated by her pediatrician and obstetrician on the benefits of breastfeeding. Her history should be reviewed for potential contraindications. If none exist, she should be encouraged to breastfeed. If she commits to breastfeeding before the baby is born, she is more likely to be successful. Involving her partner in these discussions has also been shown to improve breastfeeding success rates.

At the time of delivery, if there are no complications, the neonate should be dried and placed skin to skin on the mother's abdomen or chest for warmth and contact. Initial Apgar scores can be assigned during this process. The newborn will find his or her way to the breast and latch on. This early breastfeeding experience greatly facilitates further breastfeeding. The neonate should not be separated from the mother except for medical reasons. If an infant or mother is not medically stable enough to breastfeed immediately after birth, hand expression should be initiated within 1 hour of delivery.

During the hospital stay, the newborn should breastfeed on demand on both breasts for as long as she or he wants. Hospital policies for rooming-in greatly facilitate breastfeeding. Generally, the neonate should nurse at least 8 times a day. A healthy full-term newborn has no medical need for formula supplements. Without pacifiers or supplemental feeds, the neonate will learn to breastfeed more quickly. The mother should be counseled on appropriate latch-on, positioning of the newborn, and manual expression of milk. Breastfeeding support should be available from all involved hospital staff, and a certified lactation consultant can be quite helpful. Early supplementation with expressed colostrum should be started for infants who are at high risk of breastfeeding problems, such as those who are preterm, multiples, weigh less than 2.7 kg (<6 lb), or feeding poorly for 12 hours, as well as for those whose mothers had cesarean section, prior breast surgery, or previous breastfeeding problems. Early supplementation with expressed colostrum can decrease excessive weight loss in the infant.

Urine and stool output can be a reliable indicator of the success of breastfeeding. A successful breastfeeding neonate should urinate 3 times a day and pass stool 3 to 4 times a day by 3 to 5 days of age. By day 5 to 7 of age, the neonate should urinate 4 to 6 times a day and pass 3 to 6 stools a day. Weight loss should be monitored and should not exceed 10% of birth weight without further evaluation. Mothers whose newborns are taken to the neonatal intensive care unit must be helped with pumping or hand expressing their breasts within the first hour after delivery. By encouraging initial and frequent expression of milk, a mother's milk supply can be established even when her newborn cannot directly nurse.

During the first 6 months after birth, the only supplement to breastfeeding that is needed is vitamin D 400 IU daily started in the first few days after birth to prevent rickets. Intramuscular vitamin K to prevent hemorrhagic disease of the newborn, application of ophthalmic antibiotic ointment or silver nitrate to prevent gonorrheal infections, and hepatitis B vaccination are administered to all newborns shortly after birth (see Chapter 23).

After hospital discharge, the breastfeeding newborn should be seen by the physician at day 3 to 5 of age and again at 2 weeks of age to support breastfeeding. Early assessment may prevent many breastfeeding problems and enables the physician to intervene early if problems arise, thereby helping to prevent discontinuation of breastfeeding. New mothers need encouragement and reassurance. At each visit, the neonate should be assessed for weight, feeding schedules, voiding and stooling patterns, and jaundice. The mother's breasts should be examined for fullness, engorgement, and nipple trauma. A feeding should be observed. Mothers who are giving formula supplementation in the first weeks need help improving milk transfer and weaning formula supplements. Referral to a lactation specialist and a follow-up appointment in several days is essential.

The infant should exclusively breastfeed until 6 months of age. At that time an iron source is needed, and iron-fortified cereal can be given with a gradual introduction of other pureed foods. The recommendation is that breastfeeding continue until at least 1 year of age or as long as the mother and infant desire.

If a mother plans to return to work, she should be counseled to initiate exclusive breastfeeding and wait until the infant is approximately 4 weeks of age before introducing a bottle of expressed milk. When the mother is separated from the infant, she should pump her breasts at regular intervals. The milk can be stored at room temperature for 4 hours, in the refrigerator for up to 4 days, or in the freezer for up to 6 months (ideal) or even 12 months (acceptable) for later use. Generally, milk should be stored in 2- to 4-ounce bags or containers that are labeled with the date of expression. When the mother is back with the infant, she should put the infant to breast at the usual interval rather than using the previously expressed milk. Many mothers can work and breastfeed well past a child's first birthday.

Sometimes pediatricians are consulted about weaning the breastfed infant. There is no age at which weaning must occur, and in many cultures toddlers nurse until age 3 to 4 years. Although some infants readily give up the breast, others are more reluctant to do so. Lactation consultants may be a valuable resource at this time.

Potential Problems

Attachment

Latching-on is the first step that is essential for successful breastfeeding. Getting some infants to latch may be difficult initially because of sleepiness or fussiness when attempts are made. It is best to start feedings when the infant exhibits early feeding cues, such as licking lips or bringing hands to the mouth. Placing the infant skin to skin in a vertical position on the mother's chest while she is leaning back can stimulate reflexive infant feeding behaviors. Infants can often maneuver themselves to the nipple with a little help if they are lying on top of their mother as she reclines in bed. The newborn should be positioned with 1 hand on each side of the breast and the chin touching the breast and the nipple near the baby's nose. This allows

the infant to get as much of the areola in the mouth as possible. Causes of poor latching include poor positioning, inverted or flat nipples, ankyloglossia (ie, tongue-tie), small mandible, engorgement, or nipple confusion (ie, preference for firm bottle nipples or pacifiers). Management may consist of help with positioning, frenotomy, or use of a supplemental nursing system at the breast. A supplemental nursing system is a small tube connected to a syringe or bottle that is slid into the infant's mouth after the infant is latched onto the breast to give a supplement of expressed milk or formula while the infant breastfeeds. This can provide flow to stimulate sucking in a sleepy infant. Occasionally nipple shields are used, but these may limit nipple stimulation and cause problems with milk supply. Thus, mothers who are given shields should be followed closely and encouraged to express milk after feedings to ensure a strong supply. In any instance of difficulty with attachment, hand expression or a pump should be used to ensure frequent effective breast emptying so that milk production continues.

Sore Nipples

Breastfeeding should not be painful. If the mother is experiencing pain, the neonate is probably not latching correctly and may be crushing the nipple with his or her gums. This may cause cracked and even bleeding nipples. If the nipple is being compressed the ducts are compressed as well, resulting in poor milk transfer. The nipple may appear flat or pinched after the feeding. Pediatricians can learn a great deal about the status of breastfeeding by checking a mother's breasts for fullness and trauma. With a correct latch, neonates have the nipple and a significant portion of the areola in their mouth with their lips flanged outward. If a mother experiences pain, the newborn should be removed from the nipple and attached again. If pain persists, a medical professional should evaluate the mother-infant dyad for problems. Cracked nipples can be treated with lanolin or hydrogel pads and repositioning. Mothers should express their milk if the latch is shallow to avoid engorgement and decreased supply. Expressed milk left to dry on cracked or bleeding nipples has healing properties. In the setting of significant injury, the mother may need to pump the affected breast for 24 hours while the nipple heals. Occasionally sore nipples are secondary to a candidal or bacterial infection, atopic dermatitis, or Raynaud phenomenon (ie, vasospasm). Raynaud phenomenon can be secondary to trauma, tends to be worse when nipples get cold, and often is improved with several days of low heat.

Engorgement/Mastitis

Engorgement may occur in the setting of milk stasis for any reason. The breast appears full, firm, lumpy, and tender. Treatment is to empty the breast, and the newborn or infant is the most effective breast pump. Gentle manual compression along the posterior edge of the glandular tissue may improve emptying. Application of warm packs or taking a hot shower before feeding can be helpful. Sometimes an electric breast pump expedites emptying, softens the breast, and facilitates baby latching. If it is not possible to empty an area of the breast, such as in cases of a prior surgery that has severed some ducts, feedback inhibitor of lactation will decrease and stop milk production in this area. Postpartum engorgement may also be caused in part by interstitial edema and improved by gentle massage toward the axillary lymph nodes.

Left untreated, engorgement may result in *mastitis*, which is breast inflammation with signs of systemic infection, frequently including fever and body aches. If a mother develops mastitis, she should continue to breastfeed. Emptying the breast is important, but treatment also consists of oral antibiotics and rest. Ineffective treatment of mastitis may result in progression to a breast abscess requiring more invasive treatments, such as serial needle aspiration, drain placement, or incision and drainage. Incisions should be made parallel to ducts to avoid severing them and away from the areola so the baby can continue to latch. In cases of frank pus coming from the nipple, the baby should not breastfeed until the discharge has resolved. The mother should pump the affected breast to empty the milk and support her supply.

Low Supply

The most common reason for early cessation of breastfeeding is perceived low milk supply. Although 95% of women from developed countries are physiologically able to produce sufficient milk, many supplement with formula when it is not medically necessary. Supplementation may be done because of difficulty with latch or unrealistic expectations of newborn behavior causing a lack of confidence. Formula supplementation leads to decreased frequency of breastfeeding, and in time, milk supply decreases if the breasts are not emptied by the baby, a pump, or hand expression.

To encourage exclusive breastfeeding, medical professionals must be able to support a mother's confidence and ability to breastfeed. They must be able to assess milk transfer as well as baby hydration and weight gain. When supplementation is necessary, medical professionals must enable mothers to express their breasts; often, this milk is the only supplement necessary. Any formula supplements given in the first few days should be of limited volume and should be stopped when mothers experience lactogenesis stage 2. At office visits, if babies have been given formula unnecessarily, physicians must help families by addressing breastfeeding problems and closely following the baby's weight as supplements are decreased and eliminated. In later months, mothers may express concern over shorter feeding times, thinking that they have less milk when, in fact, infants have become more efficient eaters.

In the baby with poor weight gain, a thorough investigation must be undertaken to determine whether the difficulty stems from a problem with the baby, mother's milk supply, milk transfer, or some combination of these. It is critical to provide the baby with sufficient calories and protect the mother's supply with pumping during this time. For mothers who do lack sufficient milk, more frequent and effective emptying of the breast may solve the problem; however, if this is unsuccessful, galactagogues (ie, human milk stimulants) may be useful in some cases.

Hyperbilirubinemia/Dehydration

Ten percent of exclusively breastfed infants born via vaginal delivery and 25% of infants born via cesarean section lose more than 10% of their birth weight. Too often, infants are started on formula supplements just as mothers have increasing milk volume. For this reason, it is important to check a mother's breasts at each

visit and encourage expression of milk at each feeding if an infant requires supplementation. Neonates who lose more than 10% to 12% of their birth weight are at risk for becoming dehydrated and have an increased likelihood of significant jaundice. Increased intake is necessary, and the frequency of feeds should be increased. If a newborn is not latching on well, expressed milk can be given by syringe. Neonates should be closely monitored, and formula can be offered after human milk if milk supply is insufficient. If insufficient supply is the problem, the mother should be assisted in increasing her milk supply. Using a breast pump will increase supply because of increased demand. If the newborn appears significantly jaundiced, serum levels of bilirubin should be obtained. Physiologic jaundice is related to hepatic immaturity with decreased conjugation of bilirubin as well as decreased excretion. Breastfeeding babies tend to have increased levels of unconjugated bilirubin. Increased feeding frequently resolves the problem as hydration status improves and frequency of stooling increases. Occasionally, especially in late preterm neonates, treatment with phototherapy is necessary. Interrupting breastfeeding is neither necessary nor helpful. For a more extensive discussion of jaundice, see Chapter 126.

Resources for the Breastfeeding Mother

Many hospitals and health care organizations have lactation specialists who can assist nursing mothers and answer questions related to lactation. Health facilities may loan or rent electric breast pumps to new mothers to help establish a good supply of milk. Some mothers may choose to purchase such pumps, especially if they are planning to continue to breastfeed after returning to work. Breast pumps usually are covered by health insurance.

Access to information can also be obtained through the internet, community agencies, or international and national organizations such as La Leche League International (www.lalecheleague.org) and the Special Supplemental Nutrition Program for Women, Infants, and Children. Such agencies provide a resource to the health care professional in assisting mothers with breastfeeding.

CASE RESOLUTION

In the case presented, the mother is aware of the many benefits of breastfeeding. You examine her breasts and note normal anatomy and easily expressed colostrum. The mother should be encouraged to breastfeed and reassured that she should be able to make adequate milk with early effective breast emptying. You recommend she stop cigarette smoking completely for her own health as well as the baby's; if she is unable to do so, however, she should be advised that breastfeeding is still superior to formula. In the hospital, she should request that her newborn be placed skin to skin with her in the delivery room and continue rooming-in to breastfeed on demand. If this is not possible, she should initiate hand expression in the first hour after the birth. Reassure her that the hospital and your office will give her support and guidance with breastfeeding. Even though she is anticipating returning to work, she should initially nurse exclusively. She can begin to introduce the bottle with pumped milk at 1 to 2 months of age. Her workplace should provide an area for nursing mothers to pump and refrigerate the milk. You encourage her to explore the lactation policies at her workplace and to seek out nursing support groups.

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CHAPTER 30

Sleep: Normal Patterns and Common Disorders

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CASE STUDY

During a routine 6-month health maintenance visit, a mother states that although her 6-month-old son falls asleep very easily at approximately 10:00 pm every night while breastfeeding, he wakes every 2 to 3 hours and cries until she nurses him back to sleep. A review of the dietary history reveals that the infant is breastfed approximately every 3 hours and was begun on rice cereal 2 weeks prior to this clinic visit. His immunizations are current. The boy has no medical problems, and his physical examination is normal.

Questions

1. How old are most infants when they can begin to sleep through the night (≥5 hours at a time) without a feeding?
2. What factors contribute to frequent nighttime awaking during infancy?
3. What advice can be given to parents to facilitate an infant's sleeping through the night?
4. What are sleep disturbances experienced by older children and adolescents?
5. What advice can you give parents about helping children develop good sleep hygiene?

Sleep disorders are common during infancy, childhood, and adolescence. Getting children to go to bed, fall asleep, stay asleep, and stay in bed can be no small challenge. Parents frequently ask pediatricians about sleep-related problems at routine health maintenance visits. Age-appropriate suggestions on how to help children sleep well are usually welcomed by parents.

Epidemiology

Sleep problems occur in 20% to 30% of typically developing children and are among the most common concerns encountered in pediatric practice. Behavioral sleep problems, including bedtime refusal or resistance, delayed sleep onset, and prolonged night awaking requiring parental intervention, are the most common reasons for sleep concerns. Inadequate sleep in children negatively affects the quality of life of both the children themselves and their parents. Increased risk for obesity, mood and behavior problems, as well as impaired concentration and academic failure are some of the consequences associated with insufficient sleep in children.

Higher than normal rates of sleep disturbances are seen in children with medical, neurodevelopmental, and psychiatric disorders, such as obstructive sleep apnea (OSA), autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disability, anxiety, and depression. An estimated 25% to 50% of children with ADHD have sleep problems, especially difficulties in initiating and maintaining sleep. The relationship of ADHD and sleep problems is often complex and multidirectional. Children with ADHD have significant symptoms of impulsivity and hyperactivity that can make settling down for bed difficult. In addition, psychostimulant use has been associated with disturbed sleep; interestingly, however, it also has been shown to have the paradoxical effect of regulating children with ADHD and getting them ready for sleep.

An estimated 50% to 80% of children with ASD experience sleep-related difficulties. In typically developing children, behavioral reasons are the most common causes of insomnia. In children with ASD, however, insomnia is multifactorial. In these children, insomnia is the result of behavioral issues; medical, neurologic, and psychiatric comorbidities; and the secondary effects of medications used to manage the symptoms of ASD and the associated comorbidities.

In most Western countries, children are expected to sleep in their own beds. In many cultures, however, it is not uncommon for newborns, infants, and young children to sleep in their parents' bed (ie, the "family bed"). Bedsharing with newborns and infants younger than 10 to 12 weeks is associated with a higher incidence of sudden unexpected infant death, especially if the mother smokes. Accidental asphyxia from overlaying or the presence of soft bedding or overheating may contribute to bedsharing–related deaths. Parents should always be advised about safe sleeping practices (see Chapter 72). In older infants and children, co-sleeping is not a problem in and of itself, and the decision to co-sleep, like the decision to breast- or bottle-feed, is an entirely personal one. Most newborns and infants who share a bed with their parents have sleep-onset associations that facilitate falling asleep. Therefore, parents who share a

bed with their young children commonly must lie down with them for 20 to 30 minutes to get them to fall asleep. Several studies have shown that co-sleeping infants are 2 to 3 times more likely to experience night awaking than those who sleep alone. Furthermore, newborns and infants who are breastfeeding and bedsharing sleep the shortest periods before awaking. Parents who plan to co-sleep with their newborns and infants for only a limited period must develop a clear transition plan, such as ending this practice by 5 to 6 months of age, before infants are old enough to object excessively. For children with sleep problems, bedsharing is not a good solution. In the absence of preexisting sleep problems or psychological concerns, however, co-sleeping as a lifestyle choice has not been associated with any long-term developmental, behavioral, or psychological problems in the co-sleeping children.

Clinical Presentation

Parents may raise concerns about their child's sleep pattern during a routine health maintenance visit. However, many parents may not volunteer information about their children's sleep or may not appreciate the potential relationship between sleep problems and daytime behaviors, learning, attention, or overall health. Thus, it is important for health professionals to routinely screen children for sleep disorders.

Pathophysiology

To understand disturbances associated with sleep, it is necessary to understand the physiology of normal sleep and the development of normal sleep behavior in children.

Sleep States

Normal sleep has 2 distinct states—rapid eye movement (REM) and non–rapid eye movement (NREM) sleep. Rapid eye movement sleep develops at approximately 29 weeks of gestation and persists throughout life. It is an active, lighter stage of sleep that occurs in association with rapid eye movements. Other features of REM sleep include suppression of muscle tone; rapid, irregular pulse and respiratory rate; and body twitches. Dreams occur during REM sleep. The pattern of REM sleep noted on electroencephalography (EEG) is very similar to stage 1 NREM sleep.

Non–rapid eye movement sleep begins at approximately 32 to 35 weeks of gestation. During NREM sleep, pulse and respiratory rates are slower and more regular and body movements are minimal. Most of the restorative functions of sleep occur during this state. After the first several months after birth, NREM sleep may be divided into 3 stages. Stage 1 includes drowsiness and the beginning of sleep with slow eye movement. Stage 2 is sleep without eye movement. Stage 3 is deep sleep (also called slow-wave sleep). Each stage represents a progressively deeper state of sleep and has a characteristic EEG tracing.

The Sleep Cycle

Rapid eye movement and NREM sleep together make up the sleep cycle. Typically, the deepest sleep takes place during the first several hours of the night, with lighter stages of NREM and REM sleep occurring during most of the rest of the night. Although sleep stages are the same in infants and adults, several differences exist between the onset and duration of REM and NREM sleep in infants and adults. First, the sleep cycle is shorter in infants than in adults (50–60 minutes and 90–100 minutes, respectively), which means that infants have more periods of active REM sleep than adults. Second, the total amount of time spent in REM sleep decreases with increasing age. Full-term newborns spend approximately 50% of their total sleep time in REM sleep, whereas for preterm newborns up to 80% of total sleep time is spent in REM sleep; this decreases to approximately 30% by 3 years of age and to 20% by adulthood. Third, infants may have very little REM latency, entering their first REM cycle very shortly after falling asleep. Adults, in comparison, generally enter their first REM period approximately 90 minutes after the onset of sleep.

Melatonin, a hormone released by the pineal gland, regulates the sleep-wake cycle. It is often called the "Dracula of hormones" because peak levels occur at night. It has both hypnotic (ie, sleep promoting) and chronobiotic (ie, sleep phase-shifting) effects on the sleep-wake cycle. After melatonin is released into the bloodstream, it is taken into tissues expressing the receptors specific for melatonin and signals the body to prepare for nighttime. The pineal gland is under the control of the suprachiasmatic nucleus, which resides in the hypothalamus. When humans are exposed to light, a signal from the retina is sent to the suprachiasmatic nucleus and subsequently to the pineal gland, thereby suppressing release of melatonin.

Sleep-Wake Patterns

Sleep patterns follow a normal developmental sequence in children, and the amount of sleep children need changes with maturation (Table 30.1). Through age 12 months, infants sleep 12 to 16 hours a day. Many infants can sleep through the night (≥5 hours uninterrupted) by age 3 months, and most infants are capable of this by age 4 months. Brief arousals are a normal part of the sleep cycle at all ages, but children should be able to return to sleep on their own without requiring parental attention. Children should be able to fall asleep on their own by age 4 to 6 months. Otherwise, parental participation to fall asleep becomes required at every awaking throughout the night.

Table 30.1. Total Recommended Amount of Sleep in a 24-Hour Period by Age

Age	*Total Number of Hours*
Newborn–12 months	12–16
1–2 years	11–14
3–5 years	10–13
6–12 years	9–12
13–18 years	8–10

Adapted with permission from Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2016;12(6):785–786.

One- to 2-year-olds sleep 11 to 14 hours per day, and by age 3 to 5 years, children sleep a total of 10 to 13 hours per day. One-year-olds take 2 naps per day. This typically decreases to 1 afternoon nap by 18 to 24 months of age. Most children take an afternoon nap until 3 years of age, and some children continue this until 5 years of age. The amount of nighttime sleep children need continues to gradually decline, decreasing from approximately 12 hours during the preschool years to approximately 8 to 10 hours during adolescence.

Adolescents are often chronically sleep deprived because of a combination of biologically driven processes and modern lifestyle demands (eg, digital media use, excessive extracurricular activities). Biologically, around the time of pubertal onset, adolescents begin to experience changes in their circadian rhythm, with delay of sleep onset and wake times by up to 2 hours (ie, sleep-wake phase delay). It has been suggested that this occurs because of delayed melatonin secretion, as well as slower accumulation of sleep drive, resulting in inability to fall asleep at an appropriate bedtime. In addition, teenagers have more demands and expectations in the late afternoon, including homework and extracurricular activities, that push their bedtime later. Ultimately, adolescents are not getting the recommended 8 to 10 hours of sleep per night, which can have serious consequences, including impaired driving, academic decline, and depression. Emerging studies have demonstrated that early middle school and high school start times can interfere with total nighttime sleep in adolescents. The American Academy of Pediatrics supports delaying start times in middle schools and high schools to relieve sleep deprivation in adolescents and its associated effects. Discussion of the pathophysiology of sleep is incomplete without inclusion of the effect of electronic media. Use of electronic media in the evening hours can disrupt sleep-wake patterns because of several reasons. Media use may directly displace sleep time. Media content may cause physiologic arousal, making it difficult to fall asleep and negatively affecting overall quality of sleep. Additionally, the light emitted by the devices themselves may disrupt circadian rhythms by suppressing endogenous melatonin secretion, making it difficult to fall asleep at the desired bedtime.

Sleep Abnormalities

The etiology of sleep disorders can be complex, involving the interaction of children's temperamental characteristics, psychosocial stressors in the home, parental child-rearing philosophies, and the developmental nature of normal sleep states and sleep cycles.

Differential Diagnosis

The differential diagnosis of sleep disorders may be distinguished by problems associated with falling asleep or maintaining sleep (eg, frequent night awaking) (Box 30.1). Falling asleep may present 2 types of difficulties: problems associated with settling children to sleep and bedtime refusal.

Inappropriate sleep-onset associations and poor or inconsistent parental limit-setting are the most common reasons for difficulty settling infants and children to sleep. Inappropriate sleep-onset associations in infants are characterized by prolonged night awaking

Box 30.1. Practical Approach to the Differential Diagnosis of Sleep Disorders in Children

Difficulty Falling Asleep

Circadian and Sleep Schedule Disturbances

- Irregular sleep-wake patterns
- Advanced sleep phase
- Delayed sleep phase
- Time in bed exceeds sleep requirement
- Regular but inappropriate sleep schedules without phase shifts (eg, late evening naps)

Habits, Associations, and Expectations

- Inappropriate sleep-onset associations
- Bedtime refusal/struggles
- Poor or inconsistent limit setting

Overstimulation

Psychosocial

- Separation anxiety
- Nighttime fears (eg, of the dark, of monsters)
- Family and social stresses

Medical

- Acute illness
- Underlying medical problems
- Medications (eg, antihistamines, stimulants, codeine, anticonvulsant agents)

Difficulty Maintaining Sleep/Nighttime Awaking

Normal Variation (eg, Breastfed Infant)

Habits, Associations, and Expectations

- Inappropriate sleep-onset associations (eg, age-inappropriate night awaking for feeding)

Psychosocial

- Nighttime fears
- Family and social stresses

Medical

- Acute illness
- Underlying medical problem
- Medications

Nightmares

Arousal Disorders

- Night terrors
- Sleepwalking
- Sleep talking

Miscellaneous Sleep Disorders

Intrinsic Sleep Disorders

- Narcolepsy
- Sleep apnea (obstructive or central)
- Restless legs syndrome
- Periodic leg movements

Sleep-Wake Transition Disorders

- Head banging
- Rocking

episodes that require parental participation (eg, holding, rocking, feeding) to fall asleep. They have not learned the critical skills of self-calming and initiating sleep on their own. Because these infants do not have the self-soothing behaviors necessary to fall back to sleep after normal nighttime arousals, they also may experience nighttime awaking. Brief arousals are a normal component of sleep. Nighttime awaking is different because of the need for parental participation to resettle the infant. The problem is the difficulty that infants experience falling back to sleep on their own, not the awaking itself.

An example of an inappropriate sleep-onset association is the infant or child who needs to be breast- or bottle-fed to fall asleep. These children need to be fed before going back to sleep after normal nighttime awaking. Although they are developmentally old enough to receive all nutrition during the day, they have become conditioned to require nighttime feedings. These children are often breast- or bottle-fed until they fall asleep and only then placed in the crib. They are conditioned to require feeding to initiate sleep, and when they experience normal nighttime arousals, they require the breast or bottle to go back to sleep. Similarly, children who lack the self-comforting and self-initiating skills necessary to fall asleep on their own will awake, cry, and want to be held, comforted, or entertained before they can go back to sleep. Behavioral insomnia resulting from poor or inconsistent parental limit-setting is most common in preschool-age and older children. These children actively resist going to bed with verbal protests and multiple or repeat demands at bedtime ("curtain calls"). These children may also have difficulty settling back to sleep at night, especially if nighttime fears or anxiety contributed to their resistance to going to bed.

Acute illness also may be a cause of sleep disturbances. Children with otitis media may awake at night because of pain. They may continue to experience awaking after the infection has resolved, however, and require comforting or some sort of attention to fall asleep again.

In infants and children between the ages of 9 and 18 months, separation and separation anxiety may also affect sleep patterns. Children may cry when parents leave the room and have difficulty settling to sleep. Ability to climb out of the crib or bed can be associated with nighttime awaking in older toddlers. The transition from a crib to a bed is usually made between 2 and 3 years of age. Children who can climb out of their cribs or beds may come out of their rooms repeatedly for drinks of water, trips to the bathroom, or to sleep in the parent's or parents' bed. Such factors as nighttime fears of the dark influence sleep behaviors during the preschool years (3–5 years of age). Children's growing needs for autonomy and control over their environment may result in bedtime refusals during the toddler and preschool years.

Disorders of the sleep-wake cycle may contribute to sleep schedule irregularities. Circadian rhythms govern the regularity and degree of wakefulness and sleepiness. The circadian clock inherent in humans is not an exact 24-hour pattern but can be modified or entrained onto one by environmental cues. Parents must provide regular and consistent structure, because development of children's sleep-wake rhythms is dependent on an interaction between the child's inherent biological rhythms and the environment. Entrainment requires predictable occurrence of time cues, such as light and dark, mealtime, and bedtime. A consistent awaking time in the morning is among the most important of these cues. Time in bed exceeding actual sleep requirement is a common cause of insomnia at any age and occurs when children are expected to sleep more than is necessary.

Irregular sleep-wake cycles may occur in children living in chaotic environments with irregular mealtimes and sleep-wake schedules. A delayed sleep phase and regular but inappropriate sleep-wake schedule are the most common forms of sleep rhythm disturbance. Children with delayed sleep phase have a resetting of their circadian rhythm; they are not sleepy at bedtime and have excessive morning sleepiness. This is a common problem, because the inherent circadian clock has a cycle closer to 25, not 24, hours. This clock has not been entrained to a 24-hour schedule in these children.

One example of a regular but inappropriate sleep-wake schedule is napping at the "wrong" time (eg, a child who regularly naps at 7:00 pm for 1 hour and then has trouble going to bed at 9:00 pm). Another is seeming confusion between day and night in some infants, who sleep most of the day and stay up most of the night.

Night terrors (pavor nocturnus), sleepwalking (somnambulism), and sleep talking (somniloquism) are all forms of partial awaking that occur during deep or stage 4 NREM sleep, most often during the transition from stage 4 NREM sleep to the first REM sleep period. Sleepwalking and sleep talking usually occur during the school-age years, whereas night terrors begin during the preschool years.

Night terrors and nightmares may begin during the preschool years and may continue throughout childhood. Night terrors are different from nightmares and occur during a different stage of the sleep cycle (Table 30.2). With night terrors, children usually sit up in bed and cry or scream inconsolably for up to 15 minutes. They may appear dazed and have signs of autonomic arousal, such as tachycardia, tachypnea, and sweating. These children cannot be consoled. When they finally go back to sleep, they do not remember the event in the morning. Because parents are often frightened by the experience, they may think the child is having a seizure or is having

Table 30.2. Nightmares Versus Night Terrors

Characteristic	*Nightmare*	*Night Terror*
Time of night	Late	Early, usually within 4 hours of bedtime
Sleep stage	Rapid eye movement sleep	Partial arousal from deep non–rapid eye movement sleep
State of child	Scared but consolable	Disoriented, confused, and inconsolable
Memory of event	Clear recall of dream	Usually none
Return to sleep	Reluctant because of fear	Easily, unless fully awake
Management	Reassure child	Reassure parents

an emotional disturbance and may seek medical advice. Although attacks may be precipitated by stressful events or fatiguing daytime activities, night terrors do not indicate excessive stress or emotional disturbance in children's lives unless they recur.

Nightmares usually occur during the last third of the night during REM sleep, whereas night terrors more often take place during the early part of the night. Nightmares are scary dreams that may awaken children, who can often remember them. Children usually can be consoled by parents but are reluctant to go back to sleep because of their fears.

Excessive daytime sleepiness can be a symptom of medical problems, such as illness, narcolepsy, sleep apnea, and depression. Viral illness is perhaps the most common medical cause of such sleepiness in children. Inadequate sleep at night is another potential cause of sleepiness during the day. Screening for daytime impairments (eg, decline in academic performance, inattention) is important in children suspected of having sleep disorders. Primary sleep disorders, such as OSA, have been shown to be associated not only with excessive daytime sleepiness but also with cognitive deficits and impaired attentional capacity.

Narcolepsy, a disorder of excessive sleepiness, is characterized by an overwhelming desire to sleep during the daytime despite adequate sleep at night. Symptoms include excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucination. *Cataplexy* is an abrupt loss of muscle tone that usually is precipitated by an emotional reaction, such as laughter or anger. *Sleep paralysis* is an inability to move or speak that occurs as individuals fall asleep or awaken. Hypnagogic hallucination, which can be visual or auditory, occurs while falling asleep. Narcolepsy affects approximately 0.05% to 0.1% of the general population. The prevalence increases to 50% of family members with a positive family history for the condition. The exact genetic basis of inheritance is unknown. The age of onset is usually between 10 and 20 years. Diagnosis is often delayed or missed for months to years in some cases because not all symptoms may be present initially. Diagnosis is important, because pharmacologic therapy with central nervous system stimulants may provide some symptomatic relief.

Sleep-related breathing disorders (SRBDs) occur on a spectrum, with habitual snoring the least severe form and OSA the most severe form. Risk factors associated with the development of SRBDs include obesity, presence of chronic sinus problems, recurrent wheezing, nasal allergies, family history of OSA, and certain genetic disorders (eg, Down syndrome, Prader-Willi syndrome). *Obstructive sleep apnea in children* is a disorder of breathing during sleep that is characterized by prolonged partial upper airway obstruction or intermittent complete obstruction (ie, obstructive apnea) that disrupts normal gas exchange and sleep patterns. Risk factors for OSA include adenotonsillar hypertrophy, obesity, craniofacial anomalies, and neuromuscular disorders. Obstructive sleep apnea syndrome (OSAS) is thought to be secondary to a combination of adenotonsillar hypertrophy and reduced neuromuscular tone of the upper airway during sleep. Large tonsils and adenoid alone are not necessarily diagnostic for OSA. Symptoms include nightly snoring, often with intermittent pauses or gasps; disturbed sleep; and daytime neurobehavioral problems. Obstructive sleep apnea syndrome should be distinguished from *primary snoring*, which is defined as snoring without obstructive apnea, arousals from sleep, or abnormalities in gas exchange. Obstructive sleep apnea syndrome not only has the potential to disturb the quality of sleep but also can cause potentially serious complications, such as failure to thrive and, in severe cases, cor pulmonale.

Restless legs syndrome, or *periodic leg movements*, is characterized by uncomfortable creeping or crawling feelings, mainly occurring in the lower extremities, when the child is resting or inactive and is relieved by movement. The condition may be attributed to growing pains in younger children (see Chapter 116) and can be associated with delayed sleep onset.

Evaluation

History

Evaluation of children with sleep difficulties begins with a thorough, detailed sleep history taken from parents and, if old enough, children themselves (Box 30.2). A thorough history includes information about total daily sleep in 24 hours; daytime sleep and nighttime

Box 30.2. What to Ask

Detailed Sleep History

- Does the child have regular nap times and bedtimes, or do these depend on changing parental schedules?
- What time does the child go to bed?
- What does the child do in the hour before bedtime? Is there a consistent bedtime routine, even on weekends?
- Does the child watch television, play video games, or use the internet or mobile telephone in the hour before bed?
- Where does the child sleep (eg, ask about co-sleeping, noise, temperature)?
- Can the child fall asleep without parental participation?
- Does the child require feeding or fluids at night?
- Can you provide a detailed explanation of when the sleep problem occurs relative to bedtime and what the child does?
- How often does the sleep problem occur?
- How long has the child been having sleep problems?
- How does the parent respond?
- Does the child snore?
- When does the child wake up in the morning? Is the child difficult to awake?
- Is the child sleepy during the day?
- How much caffeine does the child consume, for example, in coffee, tea, soda, or chocolate?
- Is the child taking any medications?
- Is there a family history of sleep disturbances?
- Is there any stress within the home resulting from marital or financial difficulties that may affect the home environment and cause the child to be anxious or stressed?

sleep; the sleep environment; bedtime rituals and routines; weekday versus weekend schedules; snoring; and evening routines, including screen time. The use of a specific screening questionnaire, such as the Children's Sleep Habits Questionnaire, may facilitate the evaluation. This questionnaire is designed to screen for the most common sleep problems in children aged 4 to 12 years. It is not intended to be used to diagnose specific sleep disorders but rather to identify children who may require further evaluation. The simple screening acronym BEARS (bedtime resistance/sleep-onset delay; excessive daytime sleepiness; awaking at night; regularity, patterns, and duration of sleep; and snoring and other symptoms) can be useful as an initial screening tool to determine whether further assessment is necessary. Evaluation should also include an assessment of the child's temperament, psychological well-being, and developmental status. Children with neurodevelopmental or psychological concerns have increased rates of sleep disturbances.

Asking about evening screen time is an important component of the sleep history, because electronic media use can disrupt sleep. Increased viewing of media on mobile electronic devices, such as tablet devices and smartphones, near bedtime has been reported. Seventy-five percent of children have at least 1 technological device in their bedroom. Approximately 1 in 10 children 13 to 18 years of age is awakened after going to bed every night or almost every night by a telephone call, text message, or email. Emerging data indicate that screen time in the evening is associated with delayed sleep onset, later bedtime, shorter sleep duration, and poor overall sleep quality.

The intake of caffeinated substances in the form of coffee and energy drinks is another component of the history to consider in adolescents experiencing sleep disturbances. Between 30% and 50% of adolescents have reported consuming energy drinks, which contain not only large amounts of caffeine but also large amounts of sugar and legal stimulants that can have dangerous side effects (eg, irregular heartbeat, heart failure, anxiety, dehydration, insomnia). The recommended maximum daily caffeine intake for adolescents aged 12 through 18 years is 100 mg, that is, the amount of caffeine in a single cup of coffee.

Physical Examination

A thorough physical examination is important to rule out organic causes of sleep difficulties. Special attention should be paid to the airway and nervous system. Conditions that may alter the sleep-wake cycle include acute illness (eg, otitis media), OSA (eg, resulting from adenoidal or tonsillar hypertrophy), colic, gastroesophageal reflux, and any central nervous system disease or abnormality.

Laboratory Tests

In most cases, a detailed history and physical examination are sufficient to establish the reason for sleep disturbance; laboratory assessment is rarely necessary. If further evaluation is warranted, it should be individualized to the child's clinical presentation. Electroencephalography may be useful if a central abnormality, such as a seizure disorder, is suspected. *Polysomnography*, which is the simultaneous monitoring of EEG, electrocardiography, chin muscle tone, eye movements, and respirations during a night of sleep in a sleep laboratory, may be useful in certain children when significant sleep disturbances, such as nocturnal seizures, narcolepsy, or OSAS, are suspected. Any child with suspected SRBD (eg, history of snoring, abnormal breathing during sleep) should be evaluated for OSAS.

The use of consumer sleep technology in the form of wearable devices and downloadable programs on mobile devices for tracking sleep cycles and overall sleep quality have become increasingly popular. The accuracy of the collected data and the relation of the data to sleep disorders is unclear, however. It would be advantageous for health care professionals to be aware of the types of available consumer sleep technology applications to further the discussion of sleep-related problems. However, it does not replace a full clinical evaluation.

Management

The goal of management is to help children develop a healthy pattern of sleeping, not simply to eliminate the immediate problem. Healthy sleep associations include providing a consistent schedule of naps and bedtime, along with a pleasant bedtime routine. It is important to put newborns and infants in their crib while they are relaxed and drowsy but not already asleep. This gives them the opportunity to develop skills to put themselves to sleep. If they become accustomed to being fed or rocked until they fall asleep, they will seek the same means of falling asleep every time they normally awaken during the night. In addition, overstimulation in the evening may make settling to sleep difficult for toddlers or young children. Instead, a routine such as a bath followed by a story in the child's bedroom with a clearly defined end point when the parent leaves the child in the crib or bed sleepy but awake may help facilitate sleep. Children must learn to fall asleep on their own.

The mainstays of treatment of infants and children with inappropriate sleep-onset associations is to put them in their crib or bed when they are sleepy but awake followed by systematic ignoring (ie, "extinction") when they awake at night. Their last memory before falling asleep should not be of a parent holding or feeding them. If the crying persists, parental contact with the newborn or infant should be brief and boring (ie, nonstimulating). *Scheduled awaking* is a technique in which the infant is slightly aroused by the parent 15 to 60 minutes before an expected spontaneous awaking in an effort to prevent spontaneous awaking. Scheduled awaking may be an effective treatment alternative for some infants who awake, cry, and require parental soothing to fall back to sleep. If an infant awakes for a feeding, the parent should try to stretch the interval between waking and feeding so that the infant has an opportunity to practice self-calming techniques.

Implementation of good sleep hygiene practices is an important first step for school-age children and adolescents who are experiencing sleep problems, especially sleep-onset problems. *Sleep hygiene* refers to the establishment and maintenance of schedules and conditions conducive to healthy, restorative sleep. Good sleep hygiene practices are listed in Box 30.3. Limiting screen time, especially in the evening, is an important component of good sleep hygiene practices.

Box 30.3. Good Sleep Hygiene Practices

Environment

- Dark.
- Quiet.
- Comfortably cool.

Schedule

- Regular bedtime.
- Regular awaking time.
- Naps, if needed, should be early in the day and of a consistent time and duration.

General

- No frightening/stimulating television, video games, or stories and no vigorous physical activities in the hour before bedtime.
- Unplug and charge technology devices outside children's bedrooms to avoid surreptitious access during sleep hours.
- Limit caffeine, especially after lunchtime.
- Consistent and calming bedtime routine.
- Consistent soothing methods.
- Children put to bed drowsy but awake.

The SPOIL System (social, play, outdoor, independent work, literacy; www.screenfreeparenting.com) may be helpful in guiding parents on how to fill their child's time with activities other than screen time. The SPOIL System was developed to provide families healthier options than viewing a screen and includes opportunities for socialization, child-led free play, time in nature, helping with age-appropriate chores, and education.

Specific sleep disorders can be addressed individually. Older toddlers and preschoolers who delay going to bed or refuse to stay in their rooms at night need clear, firm limits. These children need consistent bedtime routines and nighttime interventions for when they awake. It may be necessary to install a gate in the bedroom doorway to prevent children who refuse to stay in their rooms at night from moving about the house and potentially hurting themselves or disturbing others. Parents of children who have night terrors may require reassurance that their children are not having significant emotional problems or stressors. A night-light may help alleviate the anxieties of preschoolers who are unable to sleep at night because of their fears of darkness. Disturbances of the sleep-wake schedule can be corrected over time by gradually shifting children's schedules in the desired direction. For example, in the case of a child with a delayed sleep phase who goes to bed very late, the morning wake-up time can be progressively advanced approximately 15 minutes per day, after which bedtime is progressively advance until the desired schedule is achieved.

Pharmacologic interventions should be considered only after appropriate behavior interventions have been attempted. Medications for insomnia should be used in combination with a behavioral plan that addresses sleep hygiene and unhealthy sleep practices. It may be necessary to partner with subspecialists when treating children with underlying medical, neurodevelopmental, or psychiatric disorders. It is important to carefully review the potential effects of psychotropic medications with regard to the child's sleep. Commonly used psychotropic medications in children that may affect sleep include psychostimulants, selective serotonin reuptake inhibitors, and atypical antipsychotic medications.

Medications to manage insomnia include over-the-counter preparations and prescription medications. Antihistamines, melatonin, and herbal supplements are common over-the-counter options. Antihistamines are generally well tolerated because of their rapid onset of action and relatively short half-life. However, potential adverse reactions include "paradoxical" stimulation or disinhibition, anticholinergic effects, and development of tolerance to sedation. Antihistamines are best for short-term situational use in younger children. Melatonin, which is considered a nutritional supplement by the US Food and Drug Administration (FDA), has both hypnotic and chronobiotic properties. When used as a hypnotic agent to shorten sleep-onset latency, a larger dose is given 30 to 60 minutes before bedtime, whereas when used as a chronobiotic agent, a smaller dose is given 3 to 4 hours before bedtime in an effort to shift the circadian rhythm. Currently, the long-term side effects of melatonin, including its potential for hypothalamic-gonadal axis suppression, are unclear. The FDA does not monitor over-the-counter preparations of melatonin, and the actual dose of melatonin may not be the same as listed on the label. Thus, parents may want to consider using a pharmaceutical-grade formulation of melatonin to ensure that the tablet contains the stated amount of melatonin.

Some children may require referral to a sleep specialist, especially those children in whom significant sleep disturbances, such as narcolepsy, nocturnal seizures, or OSAS, are suspected.

Prognosis

It is to parents' advantage to help their children develop healthy sleep habits rather than ignore the problems and hope that children outgrow them. Children with sleep problems in early childhood are at increased risk for sleep problems later in life.

Sleep has an important influence on mood. Emerging data indicate an association between difficulty initiating and/or maintaining sleep with depression in children and adolescents. Additionally, sleeping less than 8 hours at night seems to be associated with an increased risk for suicide attempts after controlling for confounding variables.

CASE RESOLUTION

The 6-month-old has disordered sleep associations. He has been conditioned to nighttime feedings, although he is old enough not to require them for nutrition. The physician suggests several steps the mother can take to try to solve her son's sleep problem. She can begin by gradually lengthening the interval between daytime feedings to 4 to 5 hours. When the baby cries at night, she can wait progressively longer before feeding him and then eventually eliminate the feedings altogether. He will learn to fall asleep on his own without requiring feeding.

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CHAPTER 31

Oral Health and Dental Disorders

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CASE STUDY

The parents of a 9-month-old girl bring her to the office because they are concerned that their daughter has no teeth yet. Growth and development have proceeded normally, and the physical examination is unremarkable.

Questions

1. What is the typical first tooth to erupt, and at approximately what age does that occur?
2. What is meant by "mixed dentition"?
3. When should oral hygiene using a toothbrush and fluoride toothpaste begin?
4. What groups of children are at high risk for dental caries?
5. What are the indications for the application of fluoride varnish?

Healthy teeth allow us to consume a variety of foods, from which we obtain essential nutrients. Although physicians receive limited training about teeth, given the common nature of dental problems in children it is important that pediatricians and other pediatric primary care physicians understand and can not only recognize normal and abnormal dental conditions but can implement primary and secondary prevention of dental caries and dental injuries in their practice. Well-child care visits begin in the neonatal period and continue through the end of adolescence, and at every visit opportunities exist to promote oral health and examine oral structures for timely identification of dental problems. Infancy and early childhood are critical times for the establishment of habits, both good and bad, that have the potential to affect lifelong oral health.

Epidemiology

Both dental trauma and dental caries are common in childhood. Approximately one-third of toddlers and preschool-age children and 20% of teenagers experience dental trauma—in young children typically as the result of a fall and in older children most often the result of contact sports. Occlusal abnormalities are also common in children. At least 30% of children are estimated to have moderate to severe orthodontic needs.

Dental caries is the most common chronic disease of childhood. Even so, dental decay disproportionately affects low-income individuals, resulting in earlier onset of caries, more teeth affected, more caries-related complications, and ultimately more tooth loss during adulthood because of caries. Population-based data collected from 2011 through 2014 indicate that 36% of children age 2 through 8 years in the United States had experienced caries in their primary dentition, and 57% of US children age 12 through 19 years had experienced caries in their permanent dentition. Poverty is the most important risk factor for caries, and it also affects access to professional dental care. In 2015 to 2016, the prevalence of dental caries in children age 2 through 19 years in the United States increased as family income decreased (Figure 31.1). Among youth from families living below the federal poverty level, 56.3% had any caries, compared with 34.8% for youth from families with income levels greater than 300% of the federal poverty level. Likewise, the prevalence of untreated dental caries affected 18.6% of youth from families living below the federal poverty level, compared with 7.0% of youth from families with incomes greater than 300% of the federal poverty level.

Alaska Native/American Indian (AI/AN) children have a markedly higher prevalence of caries relative to other populations in the United States. In 2014, 76% of AI/AN children age 2 to 5 years had experienced at least 1 instance of dental caries, with 47% of all AI/AN children in this age group having untreated caries. In contrast, during 2011 to 2014, 24% of all US children between 2 and 5 years of age experienced caries and approximately 11% of children in this age group had untreated caries.

Toothache, a complication of dental caries, afflicts millions of US children. In 2007, 14% of 6- to 12-year-olds had experienced a toothache within the previous 6 months. Toothache disproportionately affects children who are poor or of minority status, or who have special health care needs.

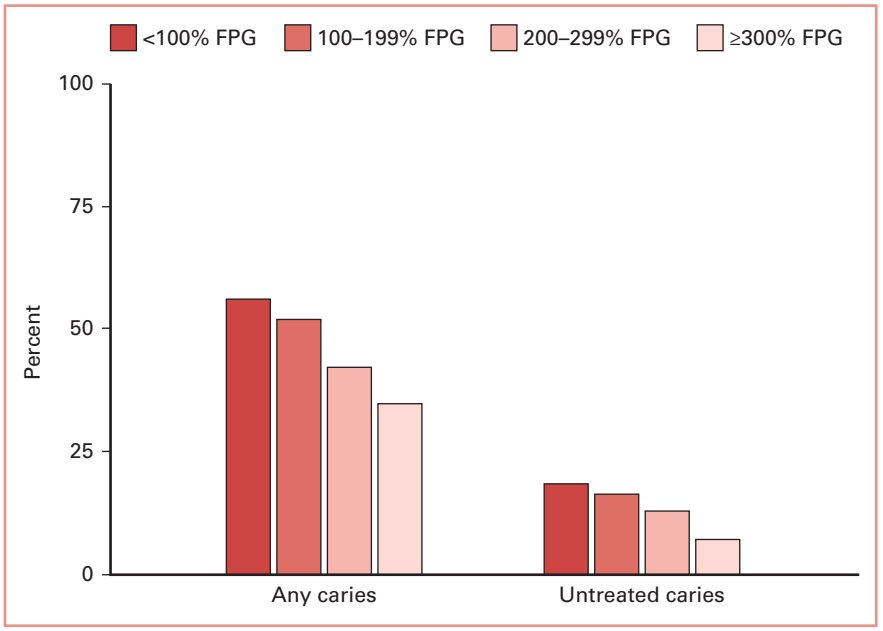

Figure 31.1. Percentage of US children, 2 to 19 years of age, with any caries and untreated caries by family income relative to Federal Poverty Guideline (FPG), 2015–2016.
Adapted from Fleming E, Afful J. Prevalence of total and untreated dental caries among youth: United States, 2015-2016. *NCHS Data Brief.* 2018;(307):1–8.

Clinical Presentation

Dental development begins in utero. Subsequently, the teeth erupt into the lower (ie, mandibular) portion of the jaw and into the upper (ie, maxillary) jaw. Teeth have a crown and root section (Figure 31.2). The crown is the visible portion of the tooth. The root is that part contained within the socket of the alveolar bone. The outer hard coating of the crown is the enamel. Beneath the enamel is the dentin, which is composed of microtubules for transport of nutrients from the pulp to the outer portions of the tooth. The pulp contains nerves and vascular structures critical for the health and viability of the tooth. Teeth are anchored to the jaw by periodontal ligaments.

Humans have 20 primary or deciduous teeth, which erupt sequentially between approximately 6 and 34 months of age (Figure 31.3A). The first primary teeth to erupt typically are the lower central incisors. These teeth erupt on average at approximately 8 months of age (±1 standard deviation: 6–10 months), after which approximately 1 tooth erupts per month until all primary teeth have erupted, by approximately 24 to 34 months of age. In each quadrant of the mouth, the normal pattern of primary tooth eruption is that the incisors erupt first, after which the first molars, the canines (ie, cuspids), and finally the second molars erupt (Table 31.1). There is variation in the timing of tooth eruption, and normal tooth eruption can vary by 6 months or more from the average age. Occasionally, the eruption process may be preceded by a bluish discoloration to the gum, called an *eruption hematoma*, which is a benign process. More often, eruption of the primary teeth is associated with more generalized symptoms, such as fussiness and drooling. These symptoms are commonly referred to as *teething*. Teething does not cause

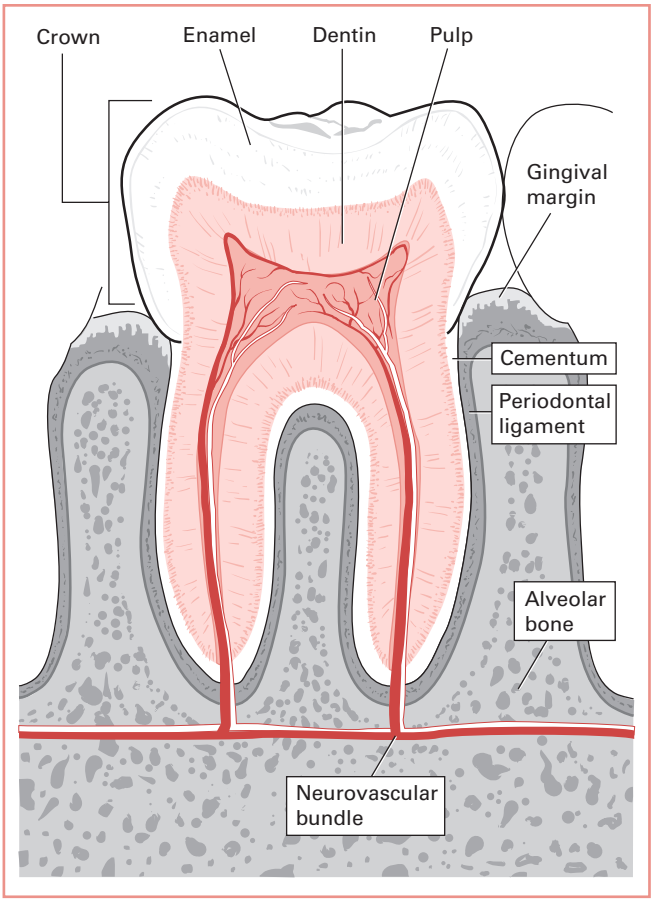

Figure 31.2. Tooth anatomy.

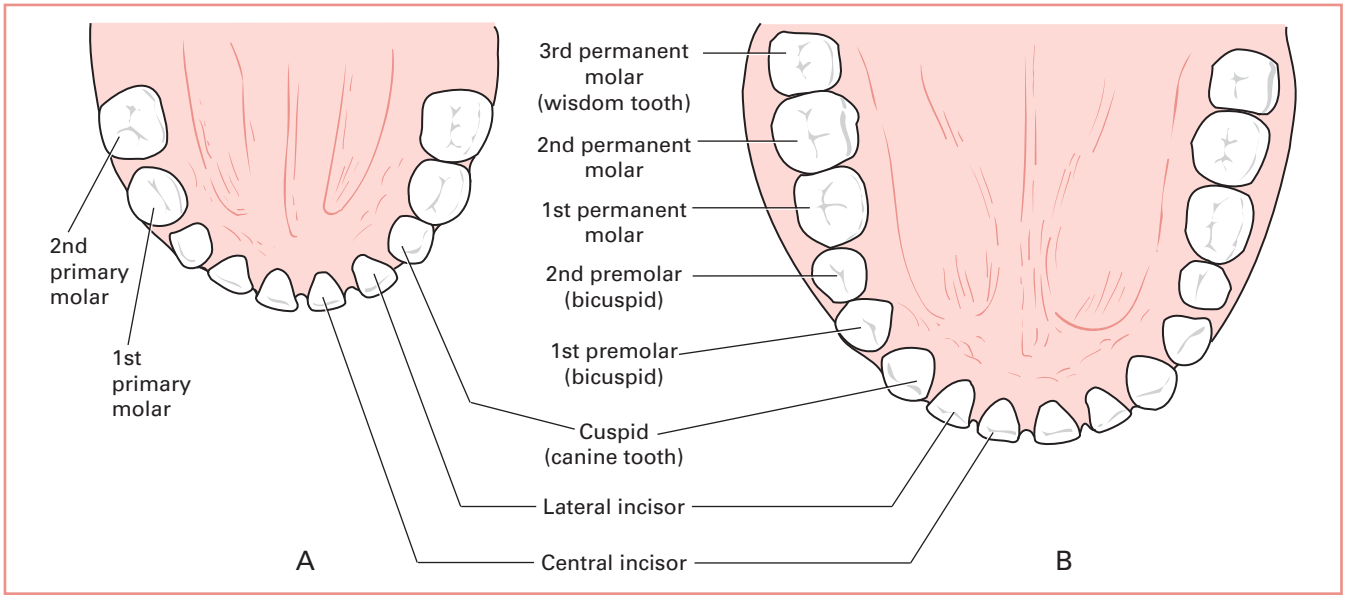

Figure 31.3. **A, Primary dentition. B, Permanent dentition.**

Table 31.1. Approximate Ages of Primary Teeth Eruption and Exfoliation in the Upper and Lower Jaws

	Erupt		*Exfoliate*	
Primary Tooth Name	*Upper*[a]	*Lower*[b]	*Upper*	*Lower*
Central incisor	8–12 months	6–10 months	6–7 years	6–7 years
Lateral incisor	9–13 months	10–16 months	7–8 years	7–8 years
Canine	16–22 months	17–23 months	10–12 years	9–12 years
First year molar	13–19 months	14–18 months	9–11 years	9–11 years
Second year molar	25–33 months	23–31 months	10–12 years	10–12 years

[a] Upper: Maxillary.
[b] Lower: Mandibular.

diarrhea, respiratory infections, or true fever, although these conditions may be present coincidentally with tooth eruption in infants.

The primary teeth are replaced by the permanent teeth (Figure 31.3B), which begin erupting at approximately 6 years of age. Permanent and primary teeth are present during the mixed dentition phase, which occurs between 6 and 13 years of age (Table 31.2). During early mixed dentition, the permanent dentition looks large and awkward relative to the remaining primary teeth, and transient malpositioning of the teeth may occur. Normally, the adult mouth has 32 permanent teeth; the last teeth to erupt are the third molars, commonly referred to as "wisdom teeth," which emerge at approximately 17 to 21 years of age.

Variations from normal in number of teeth are not uncommon. *Hypodontia* refers to the presence of fewer than normal teeth. The most common teeth to be congenitally absent are the third molars, second premolars, and maxillary lateral incisors. Congenital absence of a central incisor is distinctly uncommon and should raise concern for the presence of other midline defects. Several teeth may be missing in disorders such as Down syndrome or ectodermal dysplasia. *Anodontia* is the congenital absence of teeth. Extra teeth are called *supernumerary teeth*. Children may be born with teeth already

Table 31.2. Approximate Ages of Permanent Tooth Eruption in the Upper and Lower Jaws

	Erupt	
Permanent Tooth Name	*Upper*[a]	*Lower*[b]
Central incisor	7–8 years	6–7 years
Lateral incisor	8–9 years	7–8 years
Canine	11–12 years	9–10 years
First premolar	10–11 years	10–12 years
Second premolar	10–12 years	11–12 years
First molar	6–7 years	6–7 years
Second molar	12–13 years	11–13 years
Third molar	17–21 years	17–21 years

[a] Upper: Maxillary.
[b] Lower: Mandibular.

erupted, known as *natal teeth*. Teeth that erupt shortly after birth are referred to as *neonatal teeth* if their eruption occurs in the first month after birth. These teeth are usually incisors, and at least 90% represent normal dentition rather than supernumerary teeth. The

presence of natal or neonatal teeth may be familial and, rarely, may be suggestive of an underlying syndrome. In addition to variations in number, teeth may also demonstrate variations in color and structure resulting from abnormalities in tooth development, trauma, or extrinsic factors.

The relationship of the maxillary to the mandibular dentition has functional and aesthetic implications. *Malocclusion* is an abnormal relationship between the upper and lower teeth and may be developmental, genetic, or environmental in etiology. Children with craniofacial disorders often have significant occlusal problems and facial asymmetries necessitating early referral for care by a craniofacial team. Other children may have milder malocclusion requiring orthodontic care. Normal occlusion, or *class I occlusion*, occurs when the maxillary incisors are slightly in front of the mandibular incisors and the posterior molars interdigitate (Figure 31.4). *Class II occlusion* occurs when the maxillary teeth project too far anteriorly from the mandibular teeth. This may be associated with an overjet, commonly known as "buck teeth," which can predispose to dental injury when children fall. *Class III occlusion*, or *underbite*, occurs when the mandibular teeth are anterior to the maxillary teeth. Other common forms of malocclusion include an *anterior open bite*, whereby the posterior teeth come together but an opening exists between the top and bottom anterior teeth, and a *crossbite*, which occurs when some of the upper molars are located inside the lower molars during occlusion.

Dental injuries can be classified into tooth concussion, subluxation, luxation, avulsion, and fracture. A *concussed tooth* follows a blow that leaves the tooth tender but not displaced or mobile. *Subluxation* is loosening of a tooth after injury without displacement. With *luxation*, or displacement of the tooth from its normal position, the tooth is dislodged from its usual location; the tooth may not be mobile at all if it has been forced into adjacent bone. Luxation injuries usually result in damage to the periodontal ligament, threatening the future viability of the tooth. *Intrusion* is a form of luxation; it occurs when a tooth is driven into the bone, fracturing the alveolar socket. An intruded tooth may not be visible at all; alternatively, only the very distal aspect of the crown may emerge from the gingiva. Complete loss of the tooth from the socket is referred to as an *avulsion*.

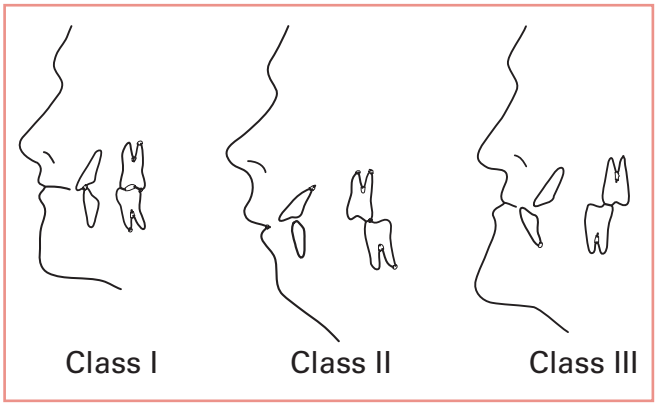

Figure 31.4. Classes of occlusion. Class I is considered most desirable from a functional and aesthetic perspective.

Dental fractures may affect the tooth crown, tooth root, and/or the alveolar bone. Fracture of the crown with no loss of tooth structure—that is, a crack exists in the tooth but no piece of tooth has broken off—is a *dental infraction*. Usually, these are initially asymptomatic. Dental follow up is needed for an infraction because the crack may allow passage of bacteria into the pulp, which can result in pulpal necrosis. Fractures involving the tooth crown, with loss of tooth structure, are classified depending on the site of the fracture. Fractures through the enamel (Ellis class I) or dentin (Ellis class II) are considered *uncomplicated dental fractures*. Fractures that involve the pulp (Ellis class 3), the root, or the alveolar bone are classified as *complicated dental fractures*.

Caries may occur any time after eruption of the teeth. *Early childhood caries* (ECC), a more general term referring to what in the past was called "baby bottle tooth decay" or "nursing bottle caries," disproportionately affects children of low socioeconomic status. The pattern of decay seen in ECC is different from that seen in the teeth of older children and adults. Typically, ECC first affects the maxillary incisors and spares the lower incisors. This pattern of decay is hypothesized to result from prolonged and frequent exposure of the teeth to sweet liquids, such as falling asleep with a juice bottle in the mouth, whereby the beverage pools around the upper incisors but the lower teeth are protected by the overlying tongue. In its earliest stages, ECC appears on physical examination as white, chalky, opaque areas at the gum line (ie, *white spot lesions*). At this early stage, the lesion is potentially reversible if remineralization can occur, such as by applying fluoride varnish to the white spots.

In older children, the pit and fissure surfaces of the molars are the likely sites of dental decay. Fermentable carbohydrates, particularly those of a sticky nature, become embedded in these surfaces and are not easily reached by the bristles of a toothbrush. This allows for prolonged action of acid-producing bacteria and subsequent caries formation. As decay invades through the layers of the tooth, it eventually reaches the pulp, resulting in inflammation and necrosis. The infection may then spread around the tooth apex, forming a periapical abscess or fistula. Dental infection can progress to involve the maxilla or mandible and then move into the fascial planes of the head and neck, producing abscess, facial cellulitis, or less commonly, airway obstruction.

Pathophysiology

Hypodontia may be familial or occur secondary to an underlying syndrome. However, failure of 1 tooth to erupt is more commonly caused by another tooth in the path of eruption or insufficient space in the dental arch. Defects of tooth structure have a variety of causes. Development of the primary teeth is predominantly subject to prenatal influences. The permanent teeth begin to develop in utero and mineralize after birth, making them susceptible to prenatal and postnatal exposures. Medications, infection, jaundice, metabolic disorders, and irradiation may adversely affect normal tooth formation or mineralization. Intrauterine infection, for example, with rubella, cytomegalovirus, or syphilis, may adversely affect tooth structure. A dental infection involving a primary tooth (eg, a periapical abscess)

can damage the developing permanent tooth bud, resulting in a malformed permanent tooth.

Discolored teeth may be the result of intrinsic or extrinsic factors. Fetal or early childhood (ie, before age 8 years) exposure to tetracycline can cause intrinsic staining of the permanent teeth. Exposure to high levels of fluoride during early childhood can cause fluorosis of the permanent dentition. Fluorosis, when it occurs in the United States, is usually mild, characterized by white striations on the permanent teeth. Children with mild fluorosis have teeth that are more resistant to dental decay. Teeth more severely affected by fluorosis may display hypoplastic enamel that is prone to staining; however, moderate and severe dental fluorosis is rare in the United States.

Inherited enamel or dentin defects may cause abnormal color of the teeth. These conditions may be isolated to the teeth, as in the case of dentinogenesis imperfecta, or as part of a systemic disorder, such as congenital erythropoietic porphyria. A single dark tooth is usually nonvital or has bled within the tooth structure after dental trauma. Extrinsic staining is superficial and is usually the result of poor oral hygiene; smoking; chewing tobacco or betel nuts; certain beverages such as coffee, tea, or wine; or medications, such as liquid iron supplements.

Malocclusion can be caused by tooth crowding, an underlying craniofacial condition, abnormal jaw growth relationship, or malpositioning of the teeth. One of the more common causes of malocclusion results from prolonged sucking of a digit (usually the thumb) or pacifier. The most common types of malocclusion associated with digit sucking are anterior open bite, overjet, and posterior crossbite.

Dental decay results from bacterial action on teeth. *Streptococcus mutans* and *Lactobacillus* species, among other bacteria, produce acids as end products of carbohydrate metabolism. These acids dissolve the calcium-phosphate mineral of a tooth's enamel during the process of demineralization. If not reversed through remineralization, the tooth's structure continues to break down until part of it collapses, resulting in a cavity. A balance of caries-promoting and caries-inhibiting factors is constantly in play. Intraoral factors that inhibit caries include normal salivary production and regular fluoride exposure; those that promote caries are frequent intake of carbohydrates, particularly simple sugars, and xerostomia (ie, dry mouth).

A variety of caries risk factors exist, some of which deserve specific mention. On a population level, children in families with low income and AN/AI children are at high risk for caries (Box 31.1). Children with developmental disabilities are also at higher risk than the general population, in part because of limited access to qualified dentists. On a family level, several genes have recently been discovered that influence caries risk. Parental oral hygiene habits, specifically less than twice daily toothbrushing by parents as well as recent maternal tooth loss from caries, increase caries risk in offspring. On an individual level, inadequate exposure to fluoride, frequent ingestion of sweetened beverages and food, use of medications that cause xerostomia, a history of caries in the previous 3 years, and visible plaque seen on oral examination are all associated with an increased risk of caries.

Box 31.1. Population and Individual Risk Factors for Dental Decay

Population Risk Factors

- Alaska Native or American Indian
- Low socioeconomic status
- Limited access to professional dental care

Family Risk Factors

- Family history of caries
- Recent maternal loss of teeth because of caries
- Parents brush teeth less than twice daily

Individual Risk Factors

- Currently active decay or personal history of caries
- Frequent and/or prolonged intake of foods containing fermentable carbohydrates (or frequent/ongoing use of liquid medications prepared with sucrose)
- Presence of visible plaque on the teeth
- Exposed root surfaces
- Having a special health care need that increases the risk for caries (eg, cleft lip), interferes with home oral hygiene (eg, oral aversiveness), or affects ability to obtain regular professional dental care (eg, behavioral difficulties associated with autism spectrum disorder)
- Inadequate exposure to fluoride
- Reduced salivary flow or xerostomia
- History of radiation therapy to head or neck
- Wearing of orthodontic appliances or prostheses

Differential Diagnosis

It can be difficult to differentiate tooth staining from a carious lesion, particularly in the tooth with small areas of discoloration on the pit and fissure surfaces. If the lesion disappears with cleaning, staining is the etiology. Staining is not always readily removed, however, and examination by a dentist and radiography can help evaluate such lesions. White spots on the teeth also can have multiple etiologies. When the white spot is chalky in appearance and located along the gingival margin, a diagnosis of demineralization should be considered. This is the earliest stage of dental decay. Small intrinsic defects of the enamel may also appear as white spots; however, these are usually located throughout the crown and not only along the gingival margin, and they usually reflect light like the rest of the tooth (ie, appearance is not chalky).

Evaluation

History

Dental pathology is diagnosed mainly through history and physical examination. The history is most important when evaluating risk for dental caries, a serious dental infection is suspected, or dental trauma has occurred. Symptoms may differentiate the degree and depth of dental injury or caries involvement of a tooth; however, young children often have difficulty localizing dental pain. A lesion

involving the dentin may produce intermittent pain, especially on exposure to temperature change or pressure on the affected tooth. After the pulp is involved, pain in the affected tooth may be severe and persistent, possibly awaking the child from sleep. In cases in which the neurovascular bundle supplying a tooth is disrupted, however, either as the result of trauma or pulpal necrosis from advanced dental caries, the pain may disappear; treatment is still necessary in these cases.

In the patient with dental injury, the history should address the mechanism of injury, the nature of other injuries, whether teeth are missing, perceived quality of pain, changes in occlusion, and tetanus immunization status.

Physical Examination

Many physicians have not traditionally included the teeth and supporting structures as part of their routine physical examination. However, pediatricians and other health professionals caring for children are generally the first, and often the only, health professionals to examine a child during the early years of life and therefore play a key role in identification of dental pathology. This is particularly true in settings in which access to routine professional dental care is limited. Early diagnosis ideally facilitates timely referral to dental specialists who provide definitive management. Additionally, children may first present to their primary care physician or an emergency department when a dental injury has occurred or an advanced odontogenic infection is present.

During each well-child care visit, the clinician should closely assess the mouth and adjacent structures for the pattern of eruption and dental development; the presence of caries, plaque, gingivitis, and other oral lesions (see Chapter 86); and malocclusion. In addition to looking for gingivitis, physicians also should examine the gingiva of children—particularly those with dental decay or toothache—to assess for evidence of periapical fistula or abscess, which typically requires antibiotic therapy or incision and drainage, followed by a root canal.

The oral cavity of a young child can be examined most easily with the caregiver and examiner in a knee-to-knee position, with the child's head in the examiner's lap and the legs wrapped around the caregiver's waist. Older children can be examined on the examination table or while seated in a chair. It is useful to have a disposable mouth mirror and a good light source. A toothbrush can be used to prop the mouth open to allow for examination of the teeth and oral cavity. The toothbrush can later be used to demonstrate good toothbrushing techniques.

In a child, occlusion is best examined by looking at the child's face from the anterior and lateral perspective and watching the child's front and back teeth as the child opens and then bites down. Having the child bite down on a tongue depressor placed horizontally between the child's upper and lower teeth demonstrates whether a cant or asymmetry of the occlusion exists. The lateral profile of a child's face can be particularly revealing. Constructing an imaginary line between the bridge of the nose, the base of the nose, and the tip of the chin defines the shape of the lateral profile. In preschool-age and older children, a slightly convex profile is preferable from functional and aesthetic perspectives. A concave profile is never normal and may be caused by midface underdevelopment or protrusion of the mandible. These children usually have a class III malocclusion. An overly convex profile may be caused by an overjet or mandibular retrusion. These children usually have a class II malocclusion.

When dental trauma occurs, the mouth and adjacent structures should first be gently cleaned. On examination, clinicians should look for facial swelling or tenderness; loose, missing, or fractured teeth; bleeding from the teeth or surrounding gums; and soft tissue injuries affecting the tongue, frena, mucosa, or palate. The presence of any of these findings suggests the need for further evaluation and treatment.

Laboratory Tests

A complete blood cell count and a blood culture should be obtained for an ill-appearing child with a dental abscess or facial cellulitis of odontogenic etiology.

Imaging Studies

Dental radiographs are useful in evaluating dental trauma and for the presence and extent of dental decay. They can also aid in determining whether an unexpectedly unerupted tooth is congenitally absent or has been prevented from erupting. If pathology is suspected, imaging, particularly panoramic radiography or computed tomography, can be useful in evaluating the facial skeleton. If a tooth or tooth fragment is missing following dental trauma, radiographic evaluation is necessary because the missing tooth or fragment may have been aspirated or swallowed; alternatively, it may have lodged in the lip or intruded into the alveolar socket, nasopharynx, or sinus cavity.

Management

Most dental disorders are definitively managed by dentists. Dental professionals are also experts in prevention of dental caries. The American Dental Association recommends that the first dental visit occur by 12 months of age. However, pediatric primary care physicians have an important role to play in identifying early and more advanced signs of dental disease and facilitating timely referral for professional dental care. Pediatric physicians may also provide initial management for odontogenic infections and dental trauma and, in cases in which access to dental care is limited, can provide treatment to halt caries progression. Some dental conditions commonly fall into the realm of the pediatric primary care physician. For example, teething symptoms can be alleviated by giving the child a cold teething toy to suck on or with acetaminophen or ibuprofen given orally. The US Food and Drug Administration has issued warnings against the use of benzocaine, viscous lidocaine, and homeopathic teething tablets for teething because these have been associated with serious or fatal side effects in young children.

Physicians and dentists can apply fluoride varnish to children at high risk for caries. Fluoride varnish is both a preventive modality and an agent used to reverse early decay in the form of white

spot lesions. Application of fluoride varnish (22,600 ppm fluoride) to the teeth can help remineralize enamel and reverse early caries lesions. Another product, silver diamine fluoride, which became available in the United States in 2015, is a solution of silver, amine, fluoride, and water that is painted onto a caries lesion to arrest more advanced active decay before it can progress to a serious infection or abscess. At 38% fluoride (44,800 ppm), it is the most concentrated fluoride product currently available for caries management. Silver diamine fluoride offers a nonsurgical alternative to traditional dental restorative surgery, and, as such, is appropriate for individuals with untreated caries who are unable to access professional dental care and others who may not be able to tolerate more extensive professional dental treatment, such as young children and special needs populations.

In most cases, advanced untreated caries in a child warrants prompt referral to a dental professional. Pulpal involvement and abscess formation may result if a carious lesion is ignored. In situations of serious dental infection in which dental care is not immediately available, antibiotics (ie, penicillin V, clindamycin) and analgesics (eg, ibuprofen) may alleviate symptoms temporarily; however, more definitive treatment (ie, root canal, extraction) is necessary to remove the source of infection and prevent resurgence of symptoms and further complications. Admission to the hospital for intravenous antibiotics and surgical drainage is usually indicated in cases in which an abscess has spread to involve the cheek, face, or neck.

Often, injuries to permanent dentition are treated differently from those to primary teeth. When permanent teeth are injured, emphasis is placed on maintaining tooth viability and prevention of complications. Even when optimal dental treatment is provided for an injured permanent tooth, however, the tooth may not survive. Blows to the teeth can result in damage to the periodontal ligament, resulting in potential neurovascular disruption, pulp necrosis, abscess formation, or root resorption. Even with prompt management of a displaced permanent tooth, a root canal may ultimately be necessary. During a root canal, the pulp is removed and the inside of the tooth is cleaned, shaped, filled, and sealed. In contrast, when a primary tooth is damaged, protecting the underlying developing permanent tooth is prioritized. For this reason, in some cases, injured or decayed primary teeth may be extracted rather than restored.

All dental injuries should be evaluated by a dental professional, but certain dental injuries, including Ellis class III fractures, root fractures, permanent tooth avulsions, and luxations, require urgent dental evaluation and management. Alveolar fractures and more complex facial fractures also require urgent consultation, usually with an oral surgeon, otolaryngologist, or plastic surgeon. It is important that pediatricians, coaches, school nurses, and parents or guardians know how to manage an avulsed permanent tooth, because survival of the tooth depends on immediate and appropriate care in the field. Primary teeth should not be reimplanted, because doing so risks damaging the underlying developing permanent dentition. A permanent tooth, however, *should* be replaced into the socket, ideally within 5 minutes of the injury, as long as the child is alert and cooperative.

The shorter the time between tooth avulsion and replacement into the socket, the better the chance for survival of the tooth. Holding the tooth by the crown (not the root, to avoid damaging the periodontal ligament fibers), an avulsed permanent tooth should be quickly rinsed with cold tap water to remove dirt and debris and then manually reimplanted in the socket. The tooth can be held in place either by the child's finger or by having the child bite onto a gauze pad or cloth until a dentist is seen. If the avulsed tooth cannot be immediately replaced into the socket, it should be stored in saline, cold milk, or a commercially available tooth-preserving system (eg, those usually stocked by paramedics and emergency departments) until definitive care is rendered. Water is not a desirable transport medium for an avulsed tooth because its low osmolality can result in cellular damage, decreasing the chance that the tooth will survive. A child with an avulsed permanent tooth should be seen urgently by a dentist for additional management, which typically involves splinting the tooth in place.

Prevention

Primary care physicians play an important role in helping families prevent dental problems (Box 31.2). Depending on the child's

Box 31.2. Caries Prevention

Standard Caries Primary Prevention for All Children

- Encourage consumption of optimally fluoridated water (0.7 ppm of fluoride).
- Initiate toothbrushing with fluoride toothpaste at first tooth eruption. Use a rice grain–size amount of toothpaste before age 2 years and a pea-size amount after 2 years. Brush twice daily and do not rinse afterward.
- Primary care physician should examine teeth and oral structures at every well-child care visit.
- Regular dental visits. The American Dental Association recommends that the first dental visit occur by 12 months of age.
- Anticipatory guidance should include the following information:
  - Frequently consuming sugar-sweetened foods and drinks (including 100% juice) increases caries.
  - Taking a bottle/sippy cup with any kind of juice or sugar-sweetened beverage to bed increases caries.
  - Regularly drinking optimally fluoridated water reduces caries.
  - Twice daily brushing with fluoride toothpaste of at least 1,000 ppm, which is all that is commercially available in the United States, reduces caries.

Intensive Caries Primary Prevention for Children With a High Risk of Caries

Includes all the standard recommendations as well as the following:

- Twice-yearly fluoride varnish application beginning at first tooth eruption.
- Initiation of regular professional dental care before 12 months of age.
- For children 5 years and older, chew polyol-sweetened gum for 10–20 minutes after meals.

age, anticipatory guidance should focus on limiting cariogenic food and beverages, toothbrushing twice daily with fluoride toothpaste, flossing, avoiding all tobacco products, preventing injury, drinking optimally fluoridated water (where available), and stressing the importance of regular professional dental care visits. Toothbrushing with fluoride toothpaste has largely supplanted fluoride drops, because fluoride toothpaste is less expensive, more readily available, and most importantly, more effective throughout the entire life span. Many aspects of oral health anticipatory guidance are also relevant to obesity prevention and promotion of overall health.

Fluoride is the single most important dental decay preventive modality. Fluoride strengthens teeth and reverses early carious lesions through enhancement of tooth mineralization. The composition of the fluoride-containing enamel, fluoride apatite, is harder and less acid soluble than the original enamel that it replaces. Increased availability of fluoridated water and fluoride-containing toothpaste has dramatically decreased the prevalence of dental caries in the United States and other countries over the past 50 years. Nevertheless, for some in the lay public, fluoride evokes controversy and concerns about adverse health effects, even though a large amount of robust research evidence attests to the safety and efficacy of fluoride for caries prevention. Pediatricians and other health professionals have an important role to play in countering misinformation and educating families about the benefits of community water fluoridation and the use of fluoride toothpaste and professionally applied fluoride products.

Caries preventive practices should begin in infancy and continue as lifelong habits; these include twice daily fluoride toothpaste for toothbrushing beginning at first tooth eruption (using a rice grain–size amount of toothpaste until age 2 years and a pea-size amount after age 2 years); drinking optimally fluoridated water where available (0.7 ppm is the recommended level of fluoride in drinking water in the United States); sound dietary practices, including avoiding frequent or prolonged exposure to fermentable carbohydrates, especially sucrose; and routine professional dental care. By the age of approximately 7 years, most children have developed sufficient fine motor skills to begin brushing their teeth independently. Until then, parents and guardians should help their children. It is also at approximately 7 years of age that children learn to spit out after toothbrushing. Some parents and guardians worry about the risks of their child swallowing fluoride toothpaste before they learn to spit. However, by applying the toothpaste to a dry toothbrush, using the appropriate amount of toothpaste, and not rinsing the mouth with water after brushing, only a small amount of fluoride is swallowed–an amount smaller than of prescription fluoride drops. There is no benefit to using a "training toothpaste" that does not contain fluoride.

It is not necessary to floss while spaces still exist between a child's teeth, as is the usual case in young children who have only primary teeth. As additional teeth erupt and teeth become closely approximated, flossing is important to remove plaque between the teeth that can contribute to caries, gingivitis, and later to periodontal disease. Sealants placed on the pit and fissure surfaces of permanent molars can also be an important defense against caries in these surfaces. Children should be seen by a dentist for evaluation for sealant placement within 6 to 12 months of eruption of their first and second permanent molars, typically occurring at approximately 6 and 12 years of age, respectively. School-based sealant programs offer an important caries preventive modality; such programs are usually provided in areas with high caries prevalence and limited availability of professional dental care. Regular use of chewing gum sweetened with polyols, also known as sugar alcohols (eg, xylitol, sorbitol, erythritol), decreases caries incidence, particularly in populations with high levels of caries. Polyols reduce caries risk through a variety of mechanisms, including stimulating saliva when chewing gum or sucking on a lozenge, substituting for sugar, and disrupting bacterial metabolism as well as biofilm organization and adherence to the teeth. The American Dental Association recommends that healthy children 5 years of age and older who are at high risk for caries chew polyol-sweetened chewing gum for 10 to 20 minutes after meals.

Certain types of malocclusion are preventable. For example, caries and dental trauma can result in premature tooth loss and subsequent loss of spacing and overcrowding, which then increase the need for orthodontic treatment. During the first year after birth, nonnutritive sucking on a digit or pacifier helps promote oral-motor development and self-soothing. Nonnutritive sucking behavior need not be discouraged up to age 1 year. However, prolonged digit or pacifier sucking contributes to malocclusion. By age 1 year, the bottle and pacifier should be discontinued, and by age 2 years, efforts should have begun to discourage digit sucking. If children can discontinue these practices before age 4 to 6 years, the malocclusion usually spontaneously reverses. Dentists can use specific devices and treatment to help stop digit sucking if other methods, including behavior modification, are unsuccessful (see Chapter 54).

Dental injuries can be prevented with appropriate vehicle restraint systems, environmental precautions when children are learning to walk and run, and use of mouthguards during certain sports. The National Federation of State High School Associations recommends mandatory mouth guards in high school football, lacrosse, ice hockey, field hockey, and wrestling. In the case of wrestling, a mouth guard is required only if the wrestler has braces. The American Dental Association recommends mouth guard use for several other sports.

Prognosis

Many dental disorders are preventable either on a primary or secondary level. Dentists can restore and repair more advanced dental disease and significant dental trauma, assuming a child has access to dental care, and ideally, has a dental home, in which an ongoing relationship exists involving the dentist, child, and parents or guardians.

Pediatric primary care physicians play an essential role in optimizing their patients' lifelong oral health by incorporating an examination of the teeth and oral structures into every physical examination, making timely referrals for prevention and in cases in which pathology is identified, including oral health prevention as part of each well-child care visit, and advocating for quality professional dental care for all patients.

CASE RESOLUTION

The parents of the infant should be reassured that the absence of teeth in their 9-month-old daughter is normal. Her first tooth may not appear for a few months. Provided she is growing and developing normally, there is no cause for concern.

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CHAPTER 32

Normal Development and Developmental Surveillance, Screening, and Evaluation

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CASE STUDY

The parents of a 12-month-old girl are concerned that she is not yet walking. They report that she sat independently at 7 months and began crawling at 8 months. She can pull herself up to stand while holding on to furniture but is not cruising. Her birth and medical history are unremarkable. The physical examination is within normal limits, and review of your records reveals no concerns on a developmental screening test administered at 9 months of age.

Questions

1. How is developmental delay in children defined?
2. What are the 5 major domains in which development is assessed?
3. How should you advise the parents in the case study about the acquisition of gross motor skills, such as walking?
4. What developmental screening tests could you administer to further assess her development?
5. What is the appropriate next step for the child with suspected developmental delay?

Development refers to the acquisition of functional skills during childhood. Monitoring the growth and development of children is an integral part of the assessment of pediatric patients. Recording the acquisition of developmental milestones provides a systematic approach by which to observe the progress of children over time. For ease of monitoring, these developmental milestones may be divided into 5 major domains or areas: gross motor, fine motor, language, social-emotional, and cognitive.

Four principles apply to all aspects of development. First, motor development is a continuous process that proceeds in the cephalocaudal direction and parallels neuronal myelination; therefore, developmental milestones reflect the maturation of the nervous system. Second, the sequence of development is the same in all children, but the rate of development may vary from child to child; for example, all children must walk before they run, but the age at which a child walks or runs varies from child to child. Third, the rate of attainment of milestones in 1 area may not parallel that in another. Fourth, certain primitive reflexes must be lost before corresponding voluntary movements can be attained (eg, the asymmetric tonic neck reflex must disappear before a child can roll over).

Pathophysiology

Development is influenced by biologic and environmental factors. Biologic factors, such as genetics, preterm birth, exposure to drugs in utero, or the presence of chronic disease, may place a child at increased risk for developmental problems and delays. Environmental factors that influence development include parental attitudes and actions, sociodemographic factors, and cultural and societal influences. The quality of parental stimulation may influence the rate of acquisition of certain skills, especially cognitive and language abilities in preschool-age children. Poverty and other socioeconomic factors may make it difficult for parents to provide their children with an optimal environment for growth and development. For example, research has found significant disparities in vocabulary and language processing between infants from families of higher– and lower–socioeconomic status (SES) as early as 18 months. Children from families of higher SES tend to have larger vocabularies at 2 years of age and score higher on language and cognition testing in elementary school. Processing speed is critical to language and cognitive development, because the faster children process (ie, understand) a word they have heard, the more cognitive energy they can put

into other parts of communication. Fortunately, regardless of SES, parents who consistently engage in language-rich activities with their infants and young children can help their children learn more quickly.

Development in Newborns and Infants

Normal, full-term newborns enter the world capable of responding to visual, auditory, olfactory, oral, and tactile stimuli. They can be quieted and can even soothe themselves. Newborns can signal needs (eg, crying when hungry or wet), but they have a limited ability to respond to caregivers, primarily exhibiting disorganized and seemingly purposeless movements when stimulated. The newborn's reflexive generalized symmetric movements (eg, arm waving and kicking) in response to environmental stimuli are eventually replaced by cortically mediated voluntary actions in older infants and children. Additionally, in newborns, certain primitive reflexes can be elicited by appropriate peripheral stimuli. Eventually, primitive reflexes are replaced by reactions that allow children to maintain postural stability in response to a variety of sensory inputs (ie, proprioceptive, visual, vestibular).

Primitive reflexes are mediated by the brain stem; they are involuntary motor responses that are elicited by appropriate peripheral stimuli and are present at birth but disappear during the first 6 months after birth. Normal motor development seems to be related to the suppression of these reflexes (Figure 32.1). Persistence or reappearance of these reflexes may indicate the presence of brain damage. Postural reactions, which are ultimately smoothly integrated into adult motor function (Figure 32.1), appear between 2 and 9 months of age. *Postural reactions* help maintain the orientation of the body in space and the interrelationship of 1 body part to another. The 3 major categories of postural reactions are righting, protection, and equilibrium.

The profile generated by combining primitive reflexes and postural reactions can be used to monitor the course of normal development and identify cases of problematic development. Persistence of primitive reflexes or failure of development of postural reactions can signal developmental problems. Authorities estimate that more than 70 primitive reflexes and postural reactions exist. Researchers do not agree on which of these reflexes or reactions are the most useful in the monitoring of development. The 7 most commonly used primitive reflexes are described in Box 32.1, and select postural reactions are presented in Box 32.2.

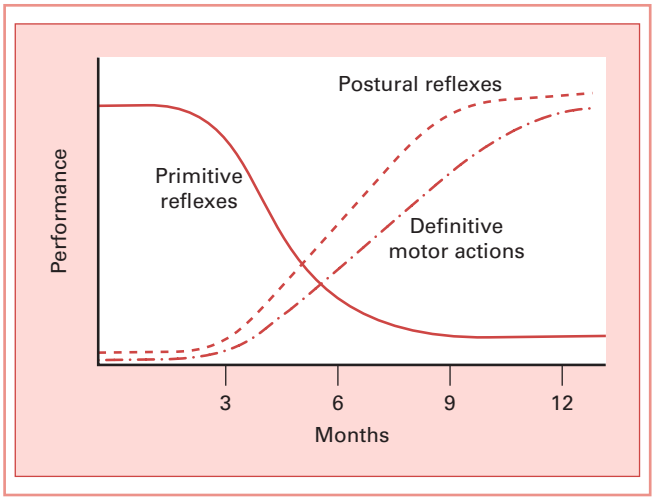

Figure 32.1. Primitive reflex profile.
Reprinted with permission from Capute AJ, Accardo PJ, Vining EP, Rubenstein JE, Harryman S. *Primitive Reflex Profile.* Baltimore, MD: University Park Press; 1978:10.

Normal Development

A developmental assessment should include an evaluation of milestones in each of the 5 major domains. *Gross motor skills* are overall movements of large muscles (eg, sitting, walking, running). *Fine motor skills* involve use of the small muscles of the hands, the ability to manipulate small objects, and eye-hand coordination. *Language skills* involve hearing and include understanding and use of language as well as nonverbal communication skills. *Social-emotional skills*

Box 32.1. The 7 Most Commonly Used Primitive Reflexes

Moro Reflex
- Allowing the baby's head to drop back suddenly results in abduction and upward movement of the arms, followed by adduction and flexion. This reflex disappears by 3–6 months of age.

Rooting Reflex
- Touching the corner of the baby's mouth results in lowering of the lower lip on the same side and movement of the tongue toward the stimulus. This reflex disappears by 3–4 months of age.

Sucking Reflex
- Placing an object in a baby's mouth causes vigorous sucking. This reflex disappears at approximately 3 months of age.

Grasp Reflex
- Placing a finger in a baby's palm causes the baby to grasp it; the baby reinforces the grip as the finger is drawn upward. A similar response is seen in the foot grasp. The palmar grasp reflex disappears by age 3–4 months and is replaced by intentional grasping by age 4–6 months; plantar grasp may be present up to 9–12 months of age.

Placing Reflex
- Stroking the anterior aspect of the tibia against the edge of a table results in the lifting of the baby's leg to step onto the table. This reflex disappears by 2 months of age.

Stepping Reflex
- Holding the baby upright and slightly leaning forward produces alternating flexion and extension movements of the legs that simulate walking. This reflex disappears by 2 months of age.

Asymmetric Tonic Neck Reflex
- With the baby lying supine, turning the head to 1 side results in extension of the extremities on that side and flexion of the opposite extremities (ie, fencing position). This reflex disappears by 3–4 months of age and allows for rolling.

Box 32.2. Select Postural Reactions

Righting Reactions

- These allow the body to maintain normal postural relationships of the head, trunk, and extremities during all activities. The different reactions appear at different ages, beginning shortly after birth and occurring up to 12 months of age.

Protection and Equilibrium Reactions

Protective Equilibrium Response

- When gently pushed toward one side while in a sitting position, infants increase trunk flexor tone toward that side to regain their center of gravity and extend the arm on the same side to protect against falling. This response usually emerges at about 4–6 months of age.

Parachute Reactions

- When held in ventral suspension and suddenly lowered (downward parachute), infants extend their arms as if to protect themselves from a fall; similar reactions are seen with forward and backward stimulation. These reactions appear at 8–9 months of age.

involve attachment, socialization, and the ability to regulate emotions. *Cognitive skills* involve the ability to use higher mental processes, including comprehension, memory, problem-solving skills, critical thinking, and logical reasoning.

Table 32.1 outlines the normal pattern of development for each of these domains. The table lists the average age of attainment of these skills as well as the normal ranges as available. Development is an orderly and sequential process, and children must proceed through several stages before any given milestone is attained. Therefore, the physician should document not only *what* a child can do but *how* the child does it. For example, to sit without support, children first achieve head control. Several stages later they can sit in a "tripod" position with arms extended in front for support, and finally, they sit with the head steady and back straight without support (Figure 32.2).

Gross Motor Skills

During the first year after birth, the ultimate goal of gross motor development is walking. The first developmental skill toward this goal is head control; by 4 months of age there should be no head lag when a child is pulled to sitting from a supine position. By 6 months of age, children can sit without support for a few seconds. At 9 to 10 months of age, children can pull themselves to a standing position, and by 12 to 18 months of age, they can walk. Children then learn to run, use stairs, hop on 1 foot, and skip—in that order.

Fine Motor

Development of the 2-finger pincer grasp is the major goal of fine motor development during the first year (Figure 32.3). The hands primarily remain in a fisted position until 3 months of age. Infants also discover the midline at this age, and shortly thereafter they may play with their hands in the midline. At age 4 months, children begin reaching for desired objects; by 6 months of age, they can transfer an object from 1 hand to the other. By 7 months, they have a 3-finger pincer grasp, and by 9 to 10 months, they have developed the 2-finger grasp, which allows them to manipulate small objects, such as raisins. By 14 months, they begin to scribble, and by 3 to 5 years, they can copy geometric shapes. Children with early preference for the use of 1 hand over another, especially before approximately 18 months of age, should be assessed for the presence of paresis or other neuromuscular problems. Handedness may manifest by 3 years but often is not firmly established until 4 to 5 years of age.

Language Skills

The development of normal speech and language skills is discussed in Chapter 33.

Social-Emotional Skills

These skills enable children to interact and respond to the surrounding world. Deficits in the development of age-appropriate social skills/social relatedness (eg, social orienting, social referencing, joint attention, pretend play) are a defining feature of autism spectrum disorder (ASD; see Chapter 132). For children on this spectrum, the development of social skills is characteristically "out of sync" with their overall level of functioning. Joint attention is the inclination to share enjoyment, interests, or achievement with other people, and like other developmental skills, it seems to manifest in graduated stages. Early skills include reciprocal smiling at the sight of a familiar person, followed by later emerging skills, such as the ability to isolate one's index finger and point with a coordinated gaze by 12 to 15 months of age. Lack of joint attention is a core deficit of ASD.

Cognitive Skills

These abilities allow children to think, reason, problem-solve, and understand the surrounding environment. *Information processing theories* address how individuals acquire, interpret, and remember information and how these abilities develop. Cognitive development involves gradual changes in these processes. Infants are born with some sensory and perceptual capabilities. Newborns are drawn to both novel and social stimuli, especially from their caregiver; these stimuli support further sensory and perception development as well as social and language development. As children develop, their attention span increases, they more efficiently process information, and they are better able to plan and direct their actions toward goals. Additionally, their knowledge base grows and becomes more integrated. These developments allow them to be more efficient learners as they age.

A child's perception and understanding of the world, including the understanding of pain, disease, and illness, are guided by the child's stage of cognitive development. The concept of object permanence or object constancy, the realization that objects may exist even if they cannot be seen, develops at approximately 7 to 9 months of age. The understanding of time comes much later. Children develop the concept of "today" at 24 months of age, "tomorrow" at 30 months, and "yesterday" at 36 months.

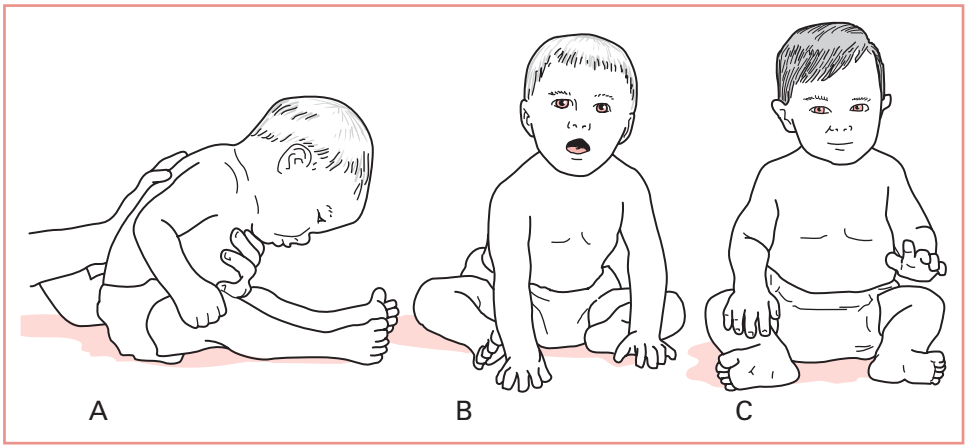

Figure 32.2. Stages in the development of sitting. A, Head control. B, "Tripod sitting." C, Head steady and back straight without support.

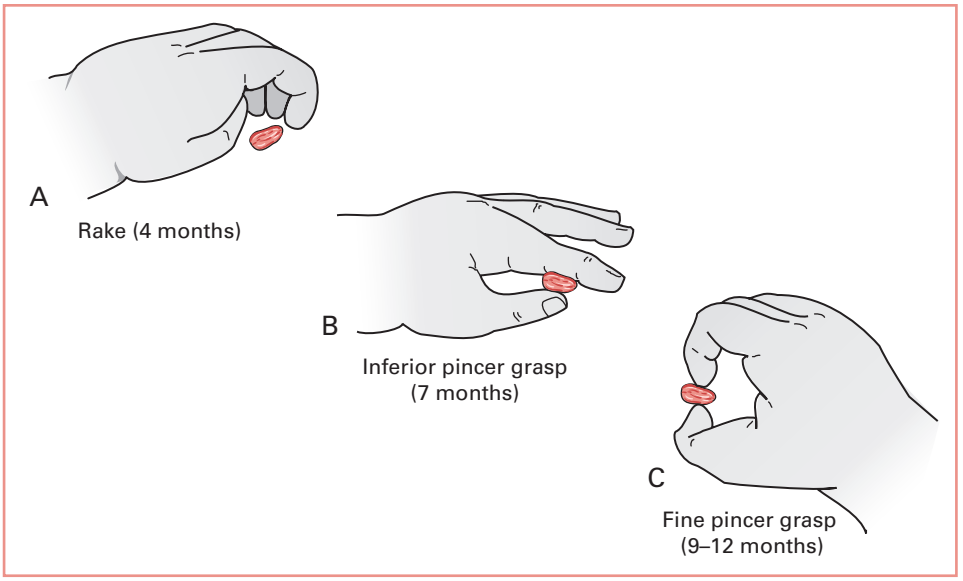

Figure 32.3. Development of the pincer grasp. A, Rake (4 months). B, Inferior pincer grasp (7 months). C, Fine pincer grasp (9–12 months).

Table 32.1. Normal Pattern of Development

Domain	*Description*	*Mean Age*	*Normal Range*
Gross motor skills	Reflex head turn; moves head side to side	Newborn	0–3 months
	Lifts head when prone	1 month	1–4 months
	Lifts shoulders up when prone	2 months	1–4 months
	Lifts up on elbows; head steady when upright	3 months	2–5 months
	Lifts up on extended hands; rolls front to back; no head lag when pulled to sitting from supine position	4 months	3–6 months
	Rolls back to front	5 months	4–7 months
	Sits independently	6 months	5–9 months
	Crawls on hands and knees	8 months	6–11 months
	Pulls to stand	9 months	6–12 months
	Cruises	11 months	9–14 months

Table 32.1. Normal Pattern of Development *(continued)*

Domain	*Description*	*Mean Age*	*Normal Range*
Gross motor skills (*continued*)	Walks	12 months	9–17 months
	Walks backward	15 months	13–17 months
	Runs	15 months	13–20 months
	Kicks a ball	24 months	18–30 months
	Walks up and down stairs using railing and putting both feet on each step; jumps with both feet off the ground; throws a ball overhand	24 months	—
	Pedals a tricycle; goes up stairs alternating feet without using the railing; balances on 1 foot for 3 seconds	3 years	30–48 months
	Hops on 1 foot 2–3 times; gallops	4 years	—
	Skips; walks down stairs using the railing and alternating feet	5 years	—
	Tandem walks	6 years	—
Fine motor	Tracks horizontally to midline	1 month	—
	Tracks past midline; tracks vertically	2 months	1–3 months
	Not fisted for >50% of the time; tracks 180°; visual threat; discovers midline	3 months	3–4 months
	Reaches for bright object; brings object to mouth	4 months	—
	Transfers object from 1 hand to the other	6 months	4–7 months
	3-finger pincer grasp	7 months	6–10 months
	Neat pincer grasp	9 months	7–12 months
	Bangs cubes in midline	9 months	7–11 months
	Tower of 2 cubes; scribbles spontaneously	14 months	14–20 months
	Drinks from a cup	15 months	10–18 months
	Uses a spoon, spilling a little	15 months	12–18 months
	Tower of 4 cubes	18 months	17–24 months
	Copies vertical and horizontal line; tower of 6 cubes	2 years	—
	Copies circle; strings beads; imitates a bridge of cubes	3 years	—
	Copies square; ties single knot; cuts basic shapes with scissors	4 years	—
	Copies triangle; draws person with 3 parts; writes first name	5 years	—
	Draws diamonds; draws person with 6 parts; forms letters correctly; creates and writes short sentences	6 years	—
Language skills[a]	Alerts to sound	Newborn	—
	Searches with eyes for sound	2 months	—
	Cooing (vowel sounds)	3 months	1–4 months
	Orients to sound/turns to voice; laughs	4 months	3–6 months
	Responds to name	4 months	4–9 months
	Babbles (consonants added to vowel sounds)	6 months	5–9 months
	Dada/Mama nonspecific	8 months	6–10 months
	Understands the word "no"	10 months	9–18 months
	Dada/Mama specific	10 months	9–14 months
	Follows 1-step command with gesture	12 months	10–16 months
	3–5–word vocabulary	12 months	—
	Follows 1-step command without gesture	15 months	12–20 months
	Points to several body parts; points to self	18 months	12–24 months
	≥50-word vocabulary (50–300 words); refers to self by name	2 years	—

(continued)

Table 32.1. Normal Pattern of Development *(continued)*

Domain	*Description*	*Mean Age*	*Normal Range*
Language skills[a] (*continued*)	2-word phrases; uses pronouns indiscriminately; follows 2-step command with gesture	2 years	20–30 months
	≥200-word vocabulary (200–1,000 words); uses 3-word sentences; speech intelligible to strangers 75% of time; uses pronouns appropriately	3 years	—
	Complex sentences using more than 1 action word (eg, "I lost my balloon because I let go"); 100% intelligible speech to strangers although may have articulation errors; points to several colors, letters and numbers when named; rote counts to 4	4 years	—
	Retells short stories with clear beginning, middle, and end; uses ≥2,000 words; produces rhyming words; rote counts to 10	5 years	—
	Knows days of the week; describes events in order	6 years	—
Social-emotional skills[b]	Regards face	Newborn	—
	Spontaneous social smile	6 weeks	1–3 months
	Discriminates social smile; relates to parent with real joy	6 months	—
	Displays stranger anxiety; plays peek-a-boo	7 months	6–9 months
	Gaze monitoring (follows adult gaze shift when adult looks away)	8 months	—
	Uses pointing to draw attention to (ie, protodeclarative) or request (ie, protoimperative) an object of interest	—	9-12 months
	Joint attention (uses 3-point gaze shifts and follows the gaze of another)	—	12–15 months
	Shows empathy (eg, looks sad when someone else cries); seeks help from adults	15 months	—
	Simple pretend play (eg, feeding doll)	18 months	17–22 months
	Helps with undressing; washes and dries hands; parallel play	2 years	22–30 months
	Undresses self; beginning to take turns	3 years	30–40 months
	Toilet training	—	24–36 months
	Imagines self as different characters; cooperative play	—	3–4 years
	Dresses without assistance; has a group of friends	5 years	—
Cognitive skills: infancy[c]	Approaches world through sensations and motor actions; attention drawn to complex or novel stimuli; growing awareness of cause and effect; development of *object permanence* (ie, awareness that object exists when removed from view); emergence of symbolic thought	—	Newborn–2 years
Cognitive Skills: early childhood	Rapidly developing language skills; limited perspective taking ability; increases in social play; ability to recall past events; growing ability to sustain attention to preferred activities	—	2–6 years
Cognitive skills: middle childhood	Able to understand that personal thoughts and feeling may differ from those of others; conservation of mass, volume, and number (eg, realization that amount stays the same if nothing is added or taken away); ability to perform mental operations if they relate to real objects; begins formal automatization of basic academic skills (eg, math facts, sight-word recognition); increased ability to focus on important information and ignore irrelevant information; use of rehearsal as the primary learning strategy	—	6–10 years
Cognitive skills: early adolescence	Able to attend to a task for an hour or more; beginning ability to engage in abstract thought and symbolic reasoning; emerging ability to use intentional learning strategies	—	10–14 years
Cognitive skills: late adolescence	Able to attend to a single task of interest for long periods; extensive and moderately integrated knowledge; more sophisticated ability to engage in abstract thought and symbolic reasoning; increasing use of self-regulatory learning strategies (eg, goal setting)	—	14–18 years
Miscellaneous cognitive milestones	Concept of today	24 months	—
	Concept of tomorrow	30 months	—
	Concept of yesterday	36 months	—
	Concept of right and left	7 years	—

[a] Detailed language milestones are presented in Chapter 33, Table 33.1.

[b] For play and social pragmatic milestones, refer to Chapter 33.

[c] Cognitive milestones adapted from constructivist theories of Jean Piaget, Lev Vygotsky, and information processing theorists.

Developmental Delay

Children are said to be developmentally delayed if they do not reach developmental milestones within the expected age range. The age ranges for these milestones are broad because of the wide variation among typically developing children. Children with global developmental delays have delays in multiple domains. Children can also have a specific delay in 1 area, such as expressive language or gross motor. Development across domains is often intertwined. Delays in 1 area can affect development in other domains. For example, a child with an expressive language delay may also demonstrate delays in social development because of limited communicative interaction with peers.

Differential Diagnosis

Three factors are involved in the differential diagnosis of children with developmental delays: determination of the area or areas of development in which delay is apparent; if motor delay is evident, determination of whether the condition is progressive or nonprogressive; and assessment for whether developmental milestones previously achieved are lost or if age-appropriate milestones were achieved at all.

The child with an early history of normal development who subsequently experiences a slowing of developmental progression, often associated with cognitive delays or seizures, may have a metabolic defect. The child who attains developmental milestones and subsequently loses them may have a neurodegenerative disease (eg, multiple sclerosis, adrenoleukodystrophy) or a lesion of the spinal cord or brain. The presence of habitual rhythmic body movements (eg, body rocking, head banging) may be a sign of a pervasive developmental disorder, such as ASD.

Cerebral palsy, the classic example of nonprogressive motor abnormality, is a form of static encephalopathy that is characterized by abnormal movement and posture. The type of cerebral palsy depends on which area of the brain is injured. Spastic cerebral palsy, which is the most common type, is secondary to upper motor neuron injury. The ataxic form of the disease is related to lesions of the cerebellum or its pathways. *Dyskinetic cerebral palsy* manifests as uncontrolled and purposeless movements that often result from a basal ganglia lesion (eg, athetosis after bilirubin deposition in the basal ganglia). Onset of symptoms is in infancy or early childhood. The key factor in making the diagnosis is establishing that the motor deficits are static and not progressing.

Evaluation

When evaluating children for possible delays in development, it is important to remember that a great deal of variation exists in the age of attainment of milestones. Additionally, the rate of acquisition of milestones in 1 area of development may not parallel that in another. Routine and ongoing assessment of a child's level of development at all periodic health maintenance visits through observation, history, physical examination, and screening tests allows the physician to form a longitudinal view of the child. The physician is thus able to identify and differentiate true deficits and delays from temporary setbacks.

History

Evaluation of children for suspected delays in development includes a complete history (Box 32.3). Family history of birth defects, childhood deaths, intellectual disability, speech delay, learning disability, and known genetic conditions (eg, fragile X syndrome) should be obtained. Perinatal factors that place children at high risk for developmental difficulties include a history of maternal drug or alcohol use during pregnancy, preterm birth of the child, and congenital infections. Preterm infants are at increased risk for developmental, behavioral, and learning disorders compared with children born at term. Although no formal guideline exists about the specific duration of time that gestational age correction should be performed for preterm infants for attainment of developmental milestone relative to term infants, most experts recommend correcting for preterm status for the first 24 months after birth. Other historical risk factors for developmental delay include history of seizures, sepsis, or meningitis; exposure to lead or other toxins; and poor feeding or growth. Environmental factors, such as stressful home conditions, history of abuse or neglect, and lack of stimulation, may also contribute to delayed development.

Physical Examination

Height and weight should be checked. Abnormal growth (ie, height or weight <5th percentile or head circumference <5th percentile or >90th percentile) may be a marker for developmental delay. The presence of congenital anomalies (eg, cataracts, hypertelorism, spina bifida) or neurocutaneous lesions (eg, café au lait spots) may be suggestive of chromosomal anomalies or other genetic diseases. Neuromuscular examination should emphasize age-appropriate milestones. Abnormalities in muscle tone (eg, hypotonia, hypertonia), bulk, or strength may be clues to the presence of neuromuscular disease (eg, muscular dystrophy), cerebral palsy, or Down syndrome.

Box 32.3. What to Ask

Normal Development in the Pediatric Patient

- Has anyone in the child's family had developmental problems or delays, or been diagnosed with learning disability, intellectual disability, or a known genetic condition?
- Did the mother use any drugs (illicit or prescription) or alcohol during pregnancy?
- Did the mother or father use illicit drugs or prescription medications prior to conception?
- Was the child born preterm?
- Does the child have a history of seizures?
- Has the child had meningitis or sepsis?
- Does the child have any history of not feeding well or of poor growth?
- Is the child's home environment characterized by any stressors (eg, new sibling, divorce, limited financial resources, homelessness)?

Laboratory Tests

Age-appropriate assessment of the child's vision and hearing should be performed if signs of motor, cognitive, or language delays are apparent. Chromosomal studies may be conducted if dysmorphic features are noted on the physical examination. Evidence of cognitive or motor delays may warrant metabolic studies (eg, organic and amino acids). Imaging studies of the head, such as magnetic resonance imaging or electroencephalography, may be necessary if the child has a history of seizures or an abnormal neurologic examination.

Developmental Surveillance, Screening, and Evaluation

Early detection of developmental delays is a responsibility of all pediatric health care professionals. Unfortunately, current detection rates of developmental disorders are lower than their actual prevalence. Approximately 20% of children between the ages of 3 and 17 years will have 1 or more developmental, learning, or emotional disorder, with 4% to 5% having developmental delays. Without the use of specific developmental screening tools, only approximately 30% of developmental disabilities are identified; however, with the use of screening tools this identification rate increases to 70% to 80%.

Developmental surveillance, the ongoing process of monitoring an individual child's developmental status, should be incorporated at each health maintenance visit. Surveillance involves eliciting and attending to parental concerns about the child's development and usually involves age-specific queries, such as whether the child is walking, talking, or pointing. Surveillance has been referred to as a sort of developmental growth chart. Recognition of the child who may be at risk of developmental delays is the goal of developmental surveillance.

Developmental screening is the administration of a brief standardized tool to identify the child at risk of a developmental disorder. Table 32.2 lists frequently used developmental screening tools. Screening is based on either parental report or direct observation and interaction with the child, and use of screening tools can increase the accuracy of clinical judgement. Developmental screening tools are not diagnostic; rather, they serve as a quick and effective means of identifying children who need further evaluation. A formal developmental screening should be performed when developmental surveillance elicits a risk factor for developmental delay; in the absence of established risk factors or parental concerns, the American Academy of Pediatrics (AAP) recommends that health professionals screen children for general development using standardized, validated tools at the 9-, 18-, and 24- or 30-month health maintenance visits. These instruments can be administered at other times if there are clinical concerns. The AAP further recommends that in addition to a general developmental screening tool, an ASD-specific screening tool should also be administered at the 18- and 24-month visits. Periodic screening is necessary to detect emerging disabilities as children grow. Screening instruments should have a broad developmental focus and be brief, inexpensive, valid, and reliable. A failed screening test should result in a referral for further developmental evaluation.

Developmental evaluation (ie, developmental assessment) is performed when surveillance or screening identifies a child as being at high risk for a developmental disorder. The aim is to identify the specific developmental disorder or disorders affecting the child. Developmental evaluation is performed by trained examiners. Unlike developmental screening, developmental evaluation is diagnostic.

The *Bayley Scales of Infant and Toddler Development®, 3rd Edition* (*Bayley-III®*), first published in 1933 by Nancy Bayley, is among the most commonly used developmental evaluation tools. It has 5 distinct scales yielding scores for 5 developmental domains: cognitive, language, motor, social-emotional, and adaptive behavior. The *Bayley-III* may be used for children 1 to 42 months of age. Especially before age 24 to 30 months, developmental tests such as the *Bayley-III*, which emphasize sensorimotor-based skills, have a poor correlation with later measures of intelligence, which emphasize language and abstract reasoning. Thus, developmental tests are best used as measures of current developmental functioning rather than as predictors of future functioning.

Intelligence tests, achievement tests, adaptive skills assessment (ie, age-appropriate skills necessary to take care of oneself and to interact with others), and behavior rating scales exist that may be used for preschool- and school-age children with suspected behavioral concerns, social-emotional concerns, learning disorders, or developmental disabilities, including intellectual disability. Delays in both cognitive skills and adaptive functioning must be present during the developmental period to make a diagnosis of *intellectual disability*.

Typical, or normal, development varies significantly; however, certain red flags, or warning signs, of developmental delay exist that warrant further monitoring or evaluation. Early detection can result in early intervention, which improves a child's chances of healthy or positive outcomes. Language development is discussed in more detail in Chapter 33, but it is important to note some red flags of language development that necessitate referral for a full evaluation, which include no babbling, no response to name, or no reciprocal gestures (eg, showing, reaching, waving) by 12 months of age; no single words by 16 months of age; and vocabulary of 50 words or less or no non-echolalic 2-word phrases by 24 months. Social-emotional development typically correlates with language development. A lack of sharing of vocalizations, back-and-forth smiles, or other facial expressions at 9 months of age; a lack of pointing to desired objects by 15 months of age; a lack of imitating actions by 2 years; or a lack of engagement in pretend play by 3 years warrants further evaluation. Motor development red flags include an inability to sit by 9 months of age, an inability to stand or bear weight at 12 months, an inability to independently walk by 18 months, frequent falling at 3 years, or poor balance at 5 years. Developmental skill regression or marked stagnation in any of the domains is a red flag and warrants further evaluation.

Management

The child with identified developmental delay in 1 or more areas should be referred to the appropriate specialist, agency, state program, or public school district (≥3 years of age) for further testing and assessment. Detailed neurologic examination may be necessary

Table 32.2. Frequently Used Developmental Screening Instruments

Assessment Type	*Instrument*	*Patient Age on Administration*	*Languages*
Parent report	Ages & Stages Questionnaire, Third Edition (ASQ-3)	1 month–5.5 years	English Spanish French Arabic Korean Vietnamese
	Child Development Inventory (CDI)	15–72 months	English Spanish
	Infant Development Inventory	Birth–18 months	English Spanish
	Parents' Evaluation of Developmental Status (PEDS)	Birth–96 months	English Spanish Vietnamese
	Parents' Evaluation of Developmental Status, Developmental Milestones (PEDS:DM)	Birth–84-132 months	English Spanish Vietnamese
	Modified Checklist for Autism in Toddlers (M-CHAT)	16–48 months	Translations in >50 languages
Direct observation and interaction with the child	Battelle Developmental Inventory, 2nd Edition (BDI-2)	Birth–95 months	English Spanish
	Bayley Infant Neurodevelopmental Screener (BINS)	3–24 months	English Spanish Portuguese
	Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®)	1–42 months	English
	Brigance® Infant & Toddler Screen	Birth–23 months	English Spanish

if gross motor delays are identified. Language delays may warrant formal hearing and speech-language assessment by an audiologist or a speech language pathologist. Cognitive impairment requires formal psychological assessment. The child aged 3 years or older and with developmental delay may qualify for special education support and services through the child's public school (see Chapter 36).

Prognosis

The pediatrician plays a key role in identifying developmental delay. When delays are observed, the pediatrician should refer for further evaluation early. Early identification of children with developmental delays is critical because it allows for early intervention. The prognosis for children with specific or global developmental delays can be greatly improved with participation in early intervention stimulation programs. Identification and management of underlying disease (eg, hypothyroidism, infection) also prevents further damage. Referring families to their state's early intervention programs can greatly stimulate the developmental potential of the child. The pediatrician can ensure that children with specific or global developmental delays receive timely support and intervention by performing developmental surveillance at each health visit and encouraging parents or caregivers to monitor milestones between visits.

CASE RESOLUTION

The parents of the child may be reassured that their child is developing normally for her age. Although most children begin walking at approximately 12 months of age, commencement of walking anytime up to age 18 months is considered to be within normal limits. The AAP recommends that standardized developmental screening be performed when developmental surveillance identifies high-risk factors for developmental delay and routinely at the 9-, 18-, and 24- or 30-month health maintenance visits. Administration of a formal screening tool is likely not necessary at this visit but can be considered again at the 15-month visit if lack of progression in the child's gross motor skills is noted or if any other risk factor is identified at that time.

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CHAPTER 33

Speech and Language Development: Normal Patterns and Common Disorders

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CASE STUDY

The parents of a 3-year-old girl bring her to see you. They are concerned because their daughter has only an 8- to 10-word vocabulary, and she does not put words together into phrases or sentences. They report that she seems to have no hearing problems; she responds to her name and follows directions well.

In general, she has been in good health. Aside from delayed speech, her development is normal. During the physical examination, which is also normal, the girl does not speak.

Questions

1. What expressive language skills should a child have by age 3 years?
2. Approximately how many words should 3-year-olds have in their vocabulary?
3. By what age should children's speech be intelligible to strangers at least 75% of the time?
4. What factors may be associated with delayed speech development?
5. What tests are used to assess children's hearing, speech, and language development?

The ability to communicate through language is a uniquely human skill. It develops in a predictable, orderly sequence, beginning in infancy with nonverbal forms and eventually progressing to the use of verbal language. When discussing the development of a child's communication skills, professionals often use the terms "speech" and "language." *Speech* refers to the articulation and production of speech sounds within the mouth, whereas *language* involves comprehension and expression; language is the understanding and use of words, phrases, and gestures to convey intent. Normal hearing is essential to the development of both speech and language.

Language is often thought of as encompassing 2 components: receptive language and expressive language. *Receptive language* refers to the ability to understand others, whereas *expressive language* is the ability to produce communication to convey meaning to others. Although most people think of language simply in terms of only receptive and expressive language, several other critical components of language development must be present for a child to develop effective communication. These include joint attention, play, and social-pragmatic language.

The development of normal speech and language skills is an important developmental milestone that is eagerly awaited by parents. Normal patterns of language development should be as familiar to pediatricians as all other aspects of child development (see Chapter 32), thereby allowing for early identification and referral for suspected delays.

The development of language skills in a normal sequence but at a slower pace than normal is referred to as *language delay;* language delays may affect only expressive language or both receptive and expressive language (eg, a mixed receptive-expressive language delay). An atypical sequence of language skill acquisition is referred to as a *language disorder*. Children with developmental language disorders have persistent and significant limitation in their ability to receive or express language.

Epidemiology

The prevalence of specific language impairment in school-age children with no hearing loss or obvious genetic or neurologic condition is approximately 7%. Speech and language disorders are more common in boys than girls and in children with a family history of language, speech, or reading disorders. Good evidence exists that early language impairment is associated with later difficulties learning to read.

Clinical Presentation

Lack of response to sound at any age, difficulty following directions, failure to achieve age-appropriate expressive language skills, reduced eye gaze or gesture, and parental concern about a child's hearing are the most important signs of hearing or language impairment. Deaf infants coo normally and may even babble; thus, an infant's vocalizing does not preclude hearing loss.

Pathophysiology

The left hemisphere of the brain is responsible for language skills in 94% of right-handed adults and in approximately 75% of left-handed adults. Peripheral auditory stimuli are transmitted to the primary auditory areas in both temporal lobes. Sounds then undergo a series of analyses, primarily in 3 main areas in the left cerebral cortex: the Wernicke area (ie, auditory association area), which is responsible for language comprehension; the Broca motor speech (ie, motor encoding) area, which is responsible for the preliminary conversion of language into motor activity; and the primary and supplementary motor cortices, which control the movements necessary for speech. This complex process is responsible for the comprehension and production of language.

For children to be successful communicators, they must be competent in all 5 critical domains of language development—joint attention, play, receptive language, expressive language, and social-pragmatic language—which are discussed herein in order of developmental progression by timing of acquisition (Figure 33.1). Additionally, a brief description of speech sound production, which also is important for successful communication, is provided.

The foundation of language development begins with eye contact, social smiling, and the ability to share attention with others, that is, *joint attention*. Use of eye gaze provides children with their first experiences with shared meaning, which is crucial to language development. Each time children look at their parent, they are provided with language learning opportunities. While looking at their parents, children begin to recognize and understand the meaning of nonverbal communication, including facial expressions and gestures. While watching a parent's mouth, they observe how speech sounds are formed. In using eye gaze, children begin to build a relationship and attachment to their parents, providing future motivation to want to communicate. Joint attention is a more advanced form of eye gaze that develops by 12 to 15 months of age. It includes sharing attention by alternating eye gaze between an object of interest, a communication partner, and back to the object. It also involves following the attention of another (eg, following the eye gaze or point of another person). Without a strong foundation in joint attention, a child will have challenges in all other language learning.

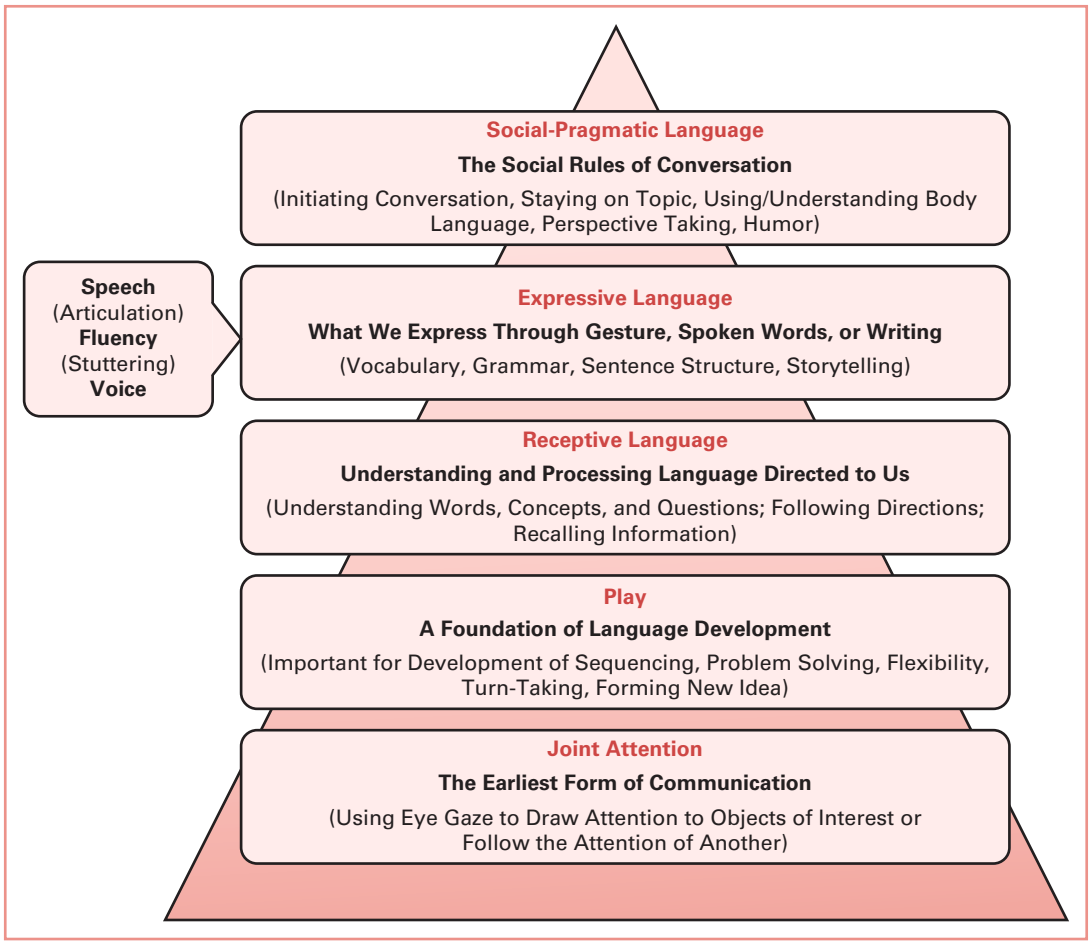


Figure 33.1. Progression of language development through the 5 domains: joint attention, play, receptive language, expressive language, and social-pragmatic language.

Children's language skills evolve primarily through parent-child interactions such as singing, reading, and play. It is within play that children learn early vocabulary, language concepts (eg, big, little, fast, slow), problem solving, organization, turn-taking, and sequencing, all of which are required for successful language use.

The ability to understand the communication of others is called *receptive language*. Early receptive milestones refer to ability to hear and respond to sound (eg, look toward a rattle being shaken), whereas later milestones reflect ability to understand spoken words, follow directions, recall spoken information, and understand questions. In typical language development, receptive language is more advanced than expressive language. Children must understand a concept before they can verbally express that same concept.

The means by which children express their thoughts and ideas through gesture, spoken words, and written communication is called *expressive language.* Early expressive milestones relate to speech production of vowels and simple consonants (eg, cooing, babbling); later, children begin to express themselves with gesture. Eventually, children use expressive language to convey their intent to others through single words; short phrases; simple sentences, including grammatical structures (eg, past tense ["-ed"]); and eventually in organized storytelling.

Social-pragmatic language refers to the way in which language is understood and used in a social context. It is the "unspoken," social rules of conversation. Development of social-pragmatic language is a long-term process that begins in infancy with a child's use of eye gaze, gesture, vocalizations, and single words to communicate with others for a variety of reasons (eg, to request, to comment, to protest, to show off, to share information). Important early milestones presenting between 9 and 12 months of age include protoimperative pointing (to request) and protodeclarative pointing (to show). Social-pragmatic language skills continue to develop and become more refined into late adolescence. Later developing skills include understanding and use of appropriate body language, initiating and maintaining conversation, staying on topic, taking the perspective of others, and using humor. Social-pragmatic language deficits are a core feature of autism spectrum disorder (ASD). Because ASD currently affects 1 in 59 children, all health professionals should be mindful of social-pragmatic language development and deficits (see Chapter 132).

For children to use language to communicate effectively, they must be intelligible to others. *Speech sound production*, which often is called "articulation," refers to how a child uses the structures of the mouth to produce speech sounds. Like language, speech sounds follow a developmental progression. Speech disorders include problems in the production of speech sounds. Speech disorders may affect articulation (ie, phonologic disorders), motor planning (ie, childhood apraxia of speech), motor strength (ie, dysarthria), fluency (ie, stuttering), or voice (ie, quality, tone, pitch, volume). By 3 years of age, a child should be at least 75% intelligible to strangers. By 4 years of age, a child should be 100% intelligible, although speech production errors (eg, "wabbit" for *rabbit*) may persist. This reflects the "rule of 4s," that is, 50% intelligible by age 2 years, 75% by age 3 years, and 100% by age 4 years.

Early language exposure through caregiver-child interaction is vital for the development of communication, cognitive, and academic skills. Earlier research reported that by the time a child is 4 years of age, a difference in word exposure of up to 30 million words may exist between children living in higher socioeconomic environments compared with those living in lower socioeconomic environments. Newer data support this finding when comparing families from socioeconomic extremes (ie, top and bottom 2% of families), although they suggest that the gap may be closer to 4 million words for families in less extreme poverty. Regardless the size, a gap exists between children living in more privileged environments and those living in more impoverished environments. Research also suggests that expressive language vocabulary at age 3 years is predictive of language and reading achievement up to 9 to 10 years of age (see Chapter 34). Knowledge of normal play as well as social-pragmatic, receptive, and expressive language skills is essential to recognition and identification of developmental delays (Table 33.1). Box 33.1 lists "danger signals" that indicate possible delays and serves as a guide for referral to specialists. The American Academy of Pediatrics reports that by age 18 months children should have an expressive vocabulary of 10 to 25 words and at age 24 months children should be using a vocabulary of at least 50 words. It is important to recognize that a vocabulary of 50 words at 24 months is not an average vocabulary size, with some children producing fewer words and some producing more words. Rather, the use of 50 words at 24 months is a minimum single word vocabulary for a child of that age. Literature in the field of speech-language pathology suggests that, on average, children 24 months of age are able to produce 200 to 300 words, with vocabulary expanding to 1,000 words by age 3 years. Thus, if a health professional sees a 24-month-old child who appears to be "struggling" to reach the 50-word milestone, language development should be monitored closely. The presence of additional language concerns or risk factors for language delay or hearing impairment warrants referral to a pediatric audiologist and pediatric speech pathologist. Children must be able to understand and express at least 50 words before they can begin combining words into 2-word combinations. It is important to remember that by age 3 years, 75% of children's speech should be intelligible to strangers.

Differential Diagnosis

The various causes of delayed language development include hearing loss, disorders of central nervous system processing, anatomic abnormalities, and environmental deprivation (Box 33.2). Although birth order (eg, the belief that younger children speak later than firstborn children because older siblings speak for them), laziness (eg, "Don't give him what he wants when he points. Make him ask for it"), and bilingualism are commonly believed to result in speech and language delay, these factors have never been proved to have a contributory role in such delay. For a complete discussion of hearing loss, refer to Chapter 88.

Disorders of central nervous system processing include global developmental delay, intellectual disability, ASD (see Chapter 132),

Table 33.1. Receptive, Expressive, Play and Social-Pragmatic Language Milestones (Birth to 5 Years)

Milestone Type	*Skill*	*Mean Age*	*Normal Range*
Receptive	Alerts to sound	Newborn	N/A
	Orients to sound/turns to voice	4 months	3–6 months
	Responds to name	4 months	4–9 months
	Understands "no"	10 months	9–18 months
	Follows 1-step command with gesture	12 months	10–16 months
	Follows 1-step command without gesture	15 months	12–20 months
	Points to several body parts	18 months	12–24 months
	Follows 2-step command with gesture	24 months	22–30 months
	Understands basic spatial terms (eg, in, on, under)	28 months	27–30 months
	Follows 3-step, unrelated directions	34 months	33–36 months
	Understands basic colors and shapes	42 months	36–48 months
Expressive	Cooing (vowel sounds)	3 months	1–4 months
	Laughs	4 months	3–6 months
	Babbling (consonants added to vowel sounds)	6 months	5–9 months
	Dada/Mama nonspecifically	8 months	6–10 months
	Dada/Mama specifically	10 months	9–14 months
	3- to 5-word vocabulary	12 months	—
	Immature jargoning (ie, gibberish with inflection)	13 months	10–18 months
	Mature jargoning (ie, gibberish with the occasional word)	18 months	16–24 months
	10- to 25-word vocabulary	18 months	—
	≥50-word vocabulary (50–300 words)	24 months (minimum)	—
	2-word phrases	24 months	20–30 months
	Uses pronouns indiscriminately	24 months	22–30 months
	States first name	34 months	30–40 months
	Uses pronouns appropriately (ie, I, you, we, me, they)	36 months	30–42 months
	≥200-word vocabulary (200–1,000 words)	3 years	—
	75% of speech intelligible to strangers	3 years	—
	3-word sentences	3 years	—
	Answers simple "WH" questions (Who, What, Where)	—	3–4 years
	Complex sentences using >1 action word (eg, "I lost my balloon because I let go")	4 years	—
	100% intelligible to strangers but may still have articulation errors	4 years	—
	Names letters or numbers	—	4–5 years
	Says rhyming words	—	4–5 years
	Tells short stories	—	4–5 years
Play[a]	Exploratory play (mouthing, shaking, banging, tapping, and squeezing toys)	—	4–10 months
	Object permanence (finds object completely hidden under blanket) and means-end behavior (pulls string to obtain desired toy)	10 months	9–12 months
	1-step pretend play (eg, pretends to drink from a cup or feed doll with bottle)	18 months	17–22 months
	Imitates housework activities	—	18–21 months
	Parallel play (ie, sharing play space with another child but not necessarily interacting)	24 months	—

Table 33.1. Receptive, Expressive, Play and Social-Pragmatic Language Milestones (Birth to 5 Years) *(continued)*

Milestone Type	*Skill*	*Mean Age*	*Normal Range*
Play[a] (*continued*)	Symbolic object use (pretend 1 object is another [eg, a banana becomes a telephone])	—	24–30 months
	Multiple-step play (eg, mix cake, bake cake, eat, and wash dishes) and imagines self as different characters (eg, firefighter, mom/dad)	—	36–42 months
	Cooperative play (ie, works together with other children for a common play goal)	—	3–4 years
Social-pragmatic[a]	Spontaneous social smile	6 weeks	1–3 months
	Dyadic joint attention (ie, infant and adult take turns exchanging looks, noises, and mouth movements)	8 weeks	6–10 weeks
	Joint attention (ie, uses 3-point gaze shifts and follows the gaze of another)	—	12–15 months
	Takes 2 turns in conversation	27 months	24–30 months
	Verbally expresses emotional and physical feelings (eg, happy, sad, sleepy, hurt)	30 months	25–36 months
	Takes 4–5 turns in conversation	40 months	36–42 months
	Theory of mind (ie, understanding another person's knowledge, beliefs, intentions, and emotions)	4 years	—
	Changes topics appropriately	—	4–5 years

Abbreviation: N/A, not applicable.

[a] Derived from Westby CE. A scale for assessing development of children's play. In: Gitlin-Weiner K, Sandgrund A, Schaefer CE, eds. *Play Diagnosis and Assessment*. 2nd ed. New York, NY: John Wiley & Sons; 2000:15–57.

Box 33.1. Danger Signals in Language Development

- Inconsistent or lack of response to auditory stimuli at any age
- Regression in language or social skills at any age
- No babbling by age 9 months
- No pointing or gesturing by age 12 months
- No intelligible single words by age 16 months
- No joint attention (ie, following the eye gaze of others) by age 15 months
- No 2-word spontaneous phrases by age 24 months
- Inability to respond to simple directions or commands (eg, "sit down," "come here") by age 24 months
- Speech predominantly unintelligible at age 36 months
- Dysfluency (ie, stuttering) of speech noticeable after age 5 years
- Hypernasality at any age
- Inappropriate vocal quality, pitch, or intensity at any age

Box 33.2. Causes of Delayed Language Development

- Hearing impairment
- Perinatal risk factors resulting in hearing impairment
- Disorders of central nervous system processing
  - Global developmental delay
  - Intellectual disability
  - Autism spectrum disorder
- Developmental language disorders
- Disorders of speech production
  - Articulation disorder
  - Dysarthria
  - Verbal apraxia
- Presence of anatomic abnormalities (eg, cleft lip, cleft palate)
- Environmental deprivation

and developmental language problems. Developmental language disorders produce speech or language delays in children in the absence of hearing loss, anatomic abnormalities of the vocal tract, intellectual disability, or global developmental delay. "Late talkers," that is, children with normal comprehension but who simply begin speaking late, have mild developmental language problems. Children who are completely nonverbal have more severe problems.

Anatomic abnormalities may also result in speech and language delays. Cleft palate is the abnormality most commonly associated with difficulties in speech production. Children with cleft palate characteristically have hypernasal speech secondary to velopharyngeal incompetence (eg, dysfunction of the soft palate). Speech sound production can also be affected as children attempt to compensate for their inability to achieve appropriate velopharyngeal closure while speaking. In addition, conductive hearing loss may result from chronic serous otitis media, which is common in children with cleft palate. The presence of a submucosal cleft palate, which is characterized by a bifid uvula, diastasis of the muscles in the midline of the soft palate with intact mucosa, and notching of the posterior

border of the hard palate, should be considered in children without an overt cleft palate who have recurrent symptomatic serous otitis media, hypernasality, and difficulties of speech production.

Environmental deprivation is another cause of delayed language development, especially in families in which children are not spoken or read to. Sometimes additional historical or physical evidence exists of deprivation (eg, profound failure to thrive, physical or sexual abuse) or emotional trauma (eg, domestic violence).

Evaluation

History

When evaluating children younger than 3 years, pediatricians must rely primarily on parental reports of children's language capabilities (Box 33.3). Children age 3 years and older usually can be engaged in conversation during the visit, but younger children are more likely to be uncooperative or remain silent when confronted by strangers or new situations. Historical factors, such as a family history of childhood deafness or speech and language delays, exposure to ototoxic agents (eg, aminoglycoside antibiotics), neonatal asphyxia or neonatal intensive care unit stay of more than 5 days, hyperbilirubinemia, maternal cocaine abuse, and low birth weight, provide valuable information in the identification of infants at high risk for delayed speech and language development (see Boxes 33.1 and 33.4).

Physical Examination

The physical examination includes a thorough assessment of the head and neck region, including examination of the hard and soft palate, to assess for the presence of overt or submucous cleft palate. Microcephaly may be an indicator for intellectual disability or structural abnormalities. Abnormalities of the external ear (eg, microtia) may be associated with sensorineural hearing loss. Otoscopic examination of the ear is an essential aspect of the examination. A middle ear effusion may be associated with conductive hearing loss. The tympanic membrane is examined for evidence of scarring or perforation, which often occurs secondary to recurrent otitis media.

Box 33.3. What to Ask

Language Development

- Are the child's language capabilities age-appropriate?
- Does the parent or do the parents feel that their child has difficulty hearing?
- Is there any family history of childhood deafness?
- Is there a family history of speech and language delays?
- Has the child been exposed to any ototoxic agents (eg, aminoglycoside antibiotics)?
- Is there a history of neonatal asphyxia, hyperbilirubinemia, or low birth weight?
- Has the child ever had bacterial meningitis?
- Did the mother have a TORCHS (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex, syphilis) infection during pregnancy?

Box 33.4. High-Risk Indicators for Hearing Loss in Children (Birth to 24 Months)

Neonatal Period (Birth–28 days)

- Family history of sensorineural hearing loss (SNHL)
- In utero infection associated with SNHL (eg, TORCHS [toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex, syphilis] infections)
- Anatomic malformations of the head and neck region
- Hyperbilirubinemia at a level requiring exchange transfusion
- Low birth weight (≤1,500 g [3.3 lb])
- Bacterial meningitis
- Low Apgar scores
- Respiratory distress (eg, meconium aspiration)
- Mechanical ventilation for ≥10 days
- Exposure to ototoxic medications (eg, aminoglycoside antibiotics) for >5 days or in combination with loop diuretics
- Stigmata of syndromes known to be associated with hearing loss (eg, Down syndrome)

Infants and Children (29 days–24 months)

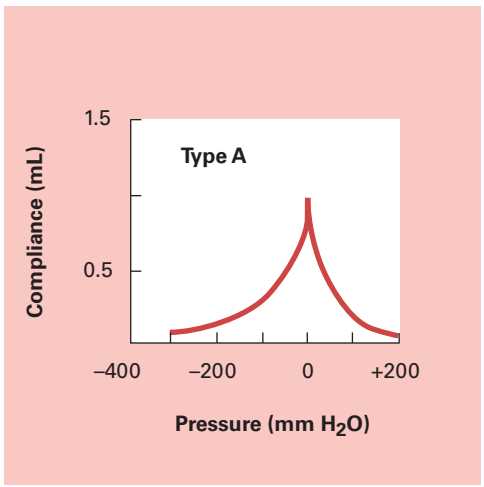
- Parental concern about hearing, speech, language, or developmental delay
- Recurrent or persistent otitis media with effusion for ≥3 months
- Severe head trauma (associated with fracture of the temporal bone)
- Infections associated with SNHL (eg, bacterial meningitis, mumps, measles)
- Neurodegenerative disorders or demyelinating diseases
- Any of the newborn risk factors listed previously

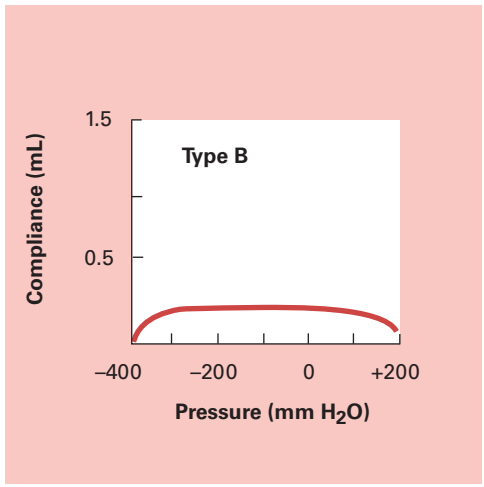
Adapted with permission from Muse C, Harrison J, Yoshinaga-Itano C, et al; American Academy of Pediatrics Joint Committee on Infant Hearing. Supplement to the JCIH 2007 position statement: principles and guidelines for early intervention after confirmation that a child is deaf or hard of hearing. *Pediatrics.* 2013;131(4):e1324–e1349 and Harlor AD Jr, Bower C; American Academy of Pediatrics Committee on Practice and Ambulatory Medicine, Section on Otolaryngology-Head and Neck Surgery. Hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics.* 2009;124(4):1252–1263.

Pneumatic otoscopy is a subjective assessment of tympanic membrane mobility (eg, compliance) when the membrane is subjected to a pulse of air. Tympanometry (eg, impedance audiometry) performed in the office can provide objective information about the mobility of the tympanic membrane and the presence of middle ear effusions (Figure 33.2). *Tympanometry* is not a hearing test; rather, it is an assessment of middle ear functioning that uses sound energy to determine the compliance of the tympanic membrane and pressure in the middle ear. Physical stigmata of any syndromes that may be associated with deafness are noted (Box 33.5).

Laboratory Tests

The advantages of early identification of hearing loss cannot be overemphasized. The Joint Committee on Infant Hearing "Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs" recommends that the hearing of all newborns should be evaluated at no later than 1 month of age. Newborns who do not pass the screening should undergo





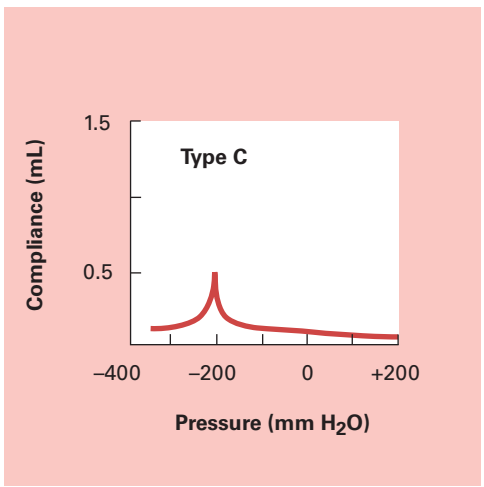


Figure 33.2. Basic tympanometry curves. The Type A curve indicates a normally compliant tympanic membrane (TM). The Type B curve indicates little or no motion of the TM and can be seen with middle ear effusion, a scarred TM, or a cholesteatoma. The Type C curve indicates negative middle ear pressure and may be seen with a resolving middle ear effusion or eustachian tube dysfunction. Other variations can occur in these basic curves that are not illustrated here.

Box 33.5. Syndromes Commonly Associated With Hearing Impairment

Autosomal-dominant Conditions

- Branchio-oto-renal syndrome
- Goldenhar syndrome (ie, oculoauriculovertebral dysplasia)
- Stickler syndrome
- Treacher Collins syndrome
- Waardenburg syndrome

Autosomal-recessive Conditions

- Alport syndrome
- Jervell and Lange-Nielsen syndrome
- Pendred syndrome
- Usher syndrome

Chromosomal Disorders

- Trisomy 13 syndrome
- Trisomy 18 syndrome

Miscellaneous Disorders

- CHARGE (coloboma, heart disease, atresia choanae, growth and intellectual disability, genitourinary tract anomalies, and ear anomalies) syndrome
- TORCHS (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis) syndrome

a comprehensive audiologic evaluation at no later than 3 months of age. High-risk indicators for hearing loss serve 2 purposes (see Box 33.4). First, in areas in which universal newborn hearing screening is not yet available, these indicators help physicians identify newborns who should undergo audiologic evaluation. Second, these risk indicators help physicians identify neonates who require ongoing medical and audiologic monitoring; normal hearing at birth in these children may not preclude the development of later hearing loss (eg, delayed onset).

Speech and language evaluation begins in the pediatrician's office, where parent report inventories may be used to validate parental concerns and office-based language assessment may be aided by the use of screening tests such as the *Clinical Linguistic and Auditory Milestone Scale* or the *Early Language Milestone Scale*. These tests are used to supplement the clinical history of a child's language abilities.

Children with suspected language delays or disorders should be referred to specialists as early as possible. The first referral should be to a pediatric audiologist to assess the child's hearing. Normal hearing is essential to the development of speech and language; thus, if any concerns exist related to the development of either, hearing loss must be ruled out. An additional referral should be made to a speech-language pathologist (SLP) for a complete speech, language, and communication assessment (eg, assessment of pragmatic language skills) (Box 33.6). An abundance of research supports the benefit of early intervention in the development of speech and language skills. If any suspicion or concern exists regarding communication development, it is best to have an SLP explore these concerns further. Taking a "wait and see" approach with families wastes valuable

Box 33.6. Role of the Speech-Language Pathologist in the Evaluation and Management of Disorder

- Speech disorders affecting intelligibility (eg, difficulty producing speech sounds, deficits in motor-planning for speech production, dysfluency or stuttering, voice disorders, resonance disorders).
- Language disorders affecting the ability to understand language or express oneself verbally or in writing.
- Social communication disorders affecting the ability to communicate for social purposes. Evaluation and treatment also may address use of eye gaze, joint attention, and play.
- Cognitive-communication disorders, including problems organizing thoughts and ideas, problem solving, planning, and remembering information.
- Swallowing disorders, including difficulty with feeding and swallowing.

time that could be used to provide intervention services to remediate speech and language deficits. It is not necessary for a child to be using any language expressively to be evaluated or treated by an SLP. Children with speech or language impairments who also exhibit signs of possible cognitive or social skills impairment should undergo a comprehensive, multidisciplinary developmental assessment conducted by experts in developmental-behavioral pediatrics, psychology, speech-language pathology, and occupational therapy.

Management

The first 3 years after birth are crucial to language development. Hearing impairment is an important cause of delayed language development in young children; thus, the Joint Committee on Infant Hearing 2007 position statement recommends that infants with confirmed hearing loss should receive appropriate interventions by 6 months of age. The history, physical examination, and initial screening can be used to suggest referral to various specialists (eg, audiologists, SLPs, child psychologists, otolaryngologists) for further clarification of hearing, speech, or language deficits and treatment. Early identification of hearing impairment and the degree of severity enable early intervention in the form of amplification of sound, special education classes for affected children, and counseling and support services for the families of affected children (see Chapter 88).

Language learning occurs best in interactive and responsive environments. Parents of infants and young children should be encouraged to have fun speaking, singing, playing with toys, and reading with their children. These reciprocal parent-child interactions, along with high verbal parental responsiveness, stimulate children cognitively and foster language development.

For bilingual children, the home language should be preserved whenever possible. Bilingualism is associated with increased cognitive control in the form of improved executive function skills and mental flexibility. Evidence indicates that bilingualism itself does not cause language delays; however, the risk for language delays exists for bilingual children as it does for monolingual children.

Special education is of prime importance in the management of children with language difficulties. The Education for All Handicapped Persons Act, which was enacted by the US Congress in 1975, and the subsequent comprehensive reauthorization of it in 1990 and revision of it in 2004 as the Individuals with Disabilities Education Act, requires that public schools provide individualized and appropriate education for all children with disabilities. Knowledge of available community resources (eg, special schools) can aid pediatricians in providing support services, such as special community agencies and support groups for children with disability and their parents. Children with language delay in the context of global developmental delay, cognitive delay, or ASD require prompt referral to early intervention services.

Prognosis

Children with a history of speech and language delays should be monitored carefully for the emergence of reading difficulties. Reading is a language-based skill that requires the appreciation of subtle differences among speech sounds (eg, phonologic awareness) and the ability to link these sounds to written symbols. The emergent literacy model of reading development assumes that reading, writing, and oral language develop concurrently based on interactions in social contexts.

Children with speech and language delays require long-term monitoring of academic, emotional, and behavioral functioning. Treated early, speech and language delays and disorders generally improve over time. The final prognosis is dependent on the nature and severity of the underlying cause and the interventions provided.

CASE RESOLUTION

The child described in the case history has delayed development of expressive language skills. At the age of 3 years, she should have a 250-word vocabulary and speak in 3-word sentences; in addition, her speech should be primarily intelligible to strangers. Because of the delay, she should be immediately referred for a hearing assessment and speech and language evaluation. Hearing loss is an important diagnosis to rule out. Simply because her parents report no hearing problems does not mean she does not have a deficit. She may have learned to respond to nonverbal cues, or she may hear only some things.

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CHAPTER 34

Literacy Promotion in Pediatric Practice

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CASE STUDY

You are seeing a 9-month-old boy for the first time for a well-child visit. The child has a completely negative history and seems to be thriving. The patient's mother works part-time as a housekeeper, and his father is a seasonal worker in agriculture. The infant is up-to-date on his immunizations. The family history is noncontributory, but his mother mentions that her 6-year-old daughter needs to repeat kindergarten. Teachers have advised the mother that her eldest daughter is cooperative, but she has not yet mastered letters and early reading. Mother says she is not concerned because the teacher said with "a little more time" her daughter will be fine.

Questions

1. How are reading and language developmentally related?
2. What are the consequences of low literacy when children get older?
3. How are literacy and health outcomes related?
4. What are the components of the Reach Out and Read model?
5. What can pediatricians do to promote literacy in families?

Early literacy promotion in the office setting is now recognized as an essential part of pediatric primary care. The American Academy of Pediatrics (AAP) and the Canadian Paediatric Society encourage health professionals to include literacy promotion in the routine clinical care of toddlers and young children. It is known from the ever-expanding evidence of early brain development that reading aloud, speaking to babies, singing, and sharing books can permanently change neuronal connections in the brain. These connections forged by reciprocal attention and spoken language are important for learning during the school years as well as for the emotional health of the child.

Literacy promotion can begin even before a baby learns to speak and long before a child is ready to learn to read. Eventual mastery of reading will depend on skills such as language ability, imagination, and familiarity with books and the reading process. Children develop many of these skills in the first few years after birth, even before they go to preschool. In fact, a child's language ability by 3 years of age is strongly correlated with later academic performance. Parent-child interactions are crucial, and guidance for parents on literacy promotion activities at home should begin within the first year after birth.

Reading aloud to children on a regular basis is among the most effective means of promoting early literacy and language development. Language skills are the foundation for later reading ability and are largely dependent on the amount and quality of language exposure. The architecture of a developing brain is physically altered by experiences during infancy. At birth, a baby's brain contains 100 billion neurons, which go on to form trillions more connections. Those connections that are stimulated by frequent use persist, and less-used synapses are eliminated as the brain matures. Reading aloud and book sharing may help ensure the preservation of brain connections associated with skills such as memory, creativity, comprehension, and language. Reading aloud is also a positive nurturing activity which in itself promotes other important neuronal connections and healthy development. The AAP recommends avoiding television or other electronic media for children younger than 2 years, because young children learn best by interacting with people.

Reading aloud exposes children to vocabulary they do not hear in daily conversations (eg, 3 bears, beanstalks). Reading aloud also stimulates the imagination (eg, cows jumping over the moon). In time, children learn that the abstract letters on the page represent words, and they become aware of different, smaller sounds that make up words. All these experiences result in reading readiness.

Consequences of Low Literacy

Low literacy has significant consequences as children age. Poor academic skills are consistently linked with higher dropout rates, entrance into the juvenile justice system, and unemployment. One-third of all juvenile offenders are reported to read below the fourth-grade level, and more than 80% of adult prison inmates are high school dropouts.

Literacy level and health outcomes are also intimately related. *Health literacy* is defined as the degree to which individuals can obtain, process, and understand the basic information they need to make appropriate health decisions. Multiple studies have demonstrated that a low literacy level negatively affects health and well-being. Compared with average or above-average health literacy, individuals with limited health literacy have a higher number of visits to emergency departments and hospitalizations, and increased morbidity.

Adolescents with low reading ability are more likely to smoke, use alcohol, carry a weapon, and be in a physical fight that results in the need for medical treatment. Conversely, higher levels of literacy are associated with positive health outcomes, such as appropriate use of inhaled asthma medication or choosing to breastfeed a baby.

Promoting literacy is good medicine not only for the individual but also for society. Aside from the societal effect of school failure, individuals with limited literacy incur medical expenses that are up to 4 times greater than patients with adequate literacy skills. Low literacy carries a high financial cost, with billions of dollars spent in the United States each year on preventable emergency department visits and hospital stays.

Literacy Promotion in the Medical Office

The AAP endorses the Reach Out and Read model of early literacy promotion, and this model is incorporated in the official AAP Bright Futures guidelines for pediatric health professionals.

The Reach Out and Read model has 3 main components:

1. Anticipatory guidance: During regular well-child visits, health professionals encourage parents to read aloud to their young children at home. The advice is age-appropriate, and concrete examples are provided or modeled by the physician (Table 34.1).
2. Books: A new developmentally and culturally appropriate book is given by the physician to patients and parents at each well-child visit so that parents have the tools to follow the physician's advice.

Table 34.1. Developmental Milestones of Early Literacy

Patient Age	*Motor Development*	*Cognition*	*What Parents Can Do*
6–12 Months	Reaches for books Book to mouth Sits in lap; holds head steady Turns pages with adult help	Looks at pictures Vocalizes, pats pictures Prefers pictures of faces	Hold the child comfortably; face-to-face gaze. Follow the baby's cues for "more" and "stop." Point to and name pictures.
12–18 Months	Sits without support May carry the book Holds the book with help Turns board pages (several at a time)	No longer mouths right away Points at pictures with 1 finger May make the same sound for a particular picture (labels) Points when asked, "Where's...?" Turns the book right side up Gives the book to an adult to read	Respond to the child's prompting to read. Let the child control the book. Be comfortable with the toddler's short attention span. Ask, "Where's the...?" and let the child point.
18–24 Months	Turns board pages easily, 1 at a time Carries the book around the house May use a book as a transitional object	Names familiar pictures Fills in words in familiar stories "Reads" to dolls or stuffed animals Recites parts of well-known stories Attention span is highly variable	Relate books to the child's experiences. Use books in routines, including bedtime. Ask the child, "What's that?" and let the child answer. Pause and let the child complete the sentence.
24–36 Months	Learns to handle paper pages Goes back and forth in books to find favorite pictures	Recites whole phrases and sometimes whole stories Coordinates text with picture Protests when the adult gets a word wrong in a familiar story Reads familiar books to self	Keep using books in routines. Read at bedtime. Be willing to read the same story over and over. Ask, "What's that?" Relate books to the child's experiences. Provide crayons and paper.
≥3 Years	Competent book handling Turns paper pages 1 at a time	Listens to longer stories Can retell familiar story Moves finger along text "Writes" own name Moves toward letter recognition	Ask, "What's happening?" Encourage writing and drawing. Let the child tell the story.

Adapted from Reach Out and Read. Milestones of early literacy development. www.reachoutandread.org/resources. Accessed February 19, 2020. Used with permission.

3. Waiting rooms: Literacy-rich waiting rooms contribute to the literacy message. Gently used books for parents to read to their child while waiting and displays or information about local libraries are encouraged. Where appropriate and feasible, community volunteers read aloud in waiting rooms, modeling for parents the pleasures and techniques of reading aloud to very young children.

Reach Out and Read had its origins in an urban clinic that served a high proportion of low-income families and has always had a special focus on children growing up in poverty. For complex reasons, poverty is a powerful predictor of children's exposure to language. Children in low-income homes are 40% less likely to be read to on a daily basis than children in higher-income households. Pioneer researchers Hart and Risley estimate that by age 4 years, children living below the poverty line hear 30 million fewer words in total than those who grow up in higher-income households.

Providing advice to parents is easiest and most effective when a book is brought in at the beginning of a visit. That way, physicians can naturally weave in guidance that is appropriate to the age of the child (Box 34.1 and Table 34.1). Advice should be brief and to the point, supportive, and part of a general conversation about the child's development and behavior.

Another advantage of presenting the book early in the visit is the amount of developmental and relationship information that can be observed by the health professional. The book is a tool that can speed informal developmental surveillance. If a 2-year-old exclaims, "Doggie says bow-wow!" there is no doubt she is putting 2 words together. If a 1-year-old uses an index finger to point and looks to see if his mother is watching, the physician can gain information about fine motor ability and the child's social interaction in only a few moments.

Children benefit from storytelling and book time in whatever fashion is most comfortable for the parent. Ideally books should be either in the family's preferred language or bilingual. It is best for parents to use the language that is easiest for them, because it is more important for children to hear a language with rich vocabulary and complex sentences than to learn English first. If no book is available in the family's native language or parents are not confident with their own reading skills, the primary care physician should encourage parents to look at books, name pictures, and talk about what is going on in the pictures with their children. Physician knowledge of local programs for adult literacy and English as a second language is often useful, because parents may ask for resources when literacy is discussed in the examination room.

Box 34.1. Anticipatory Guidance for Parents[a]

- *Newborns and very young babies* need to hear a parent's voice as much as possible: talking, singing, and telling stories are all good.
- *6-month-olds* may put books in their mouths; this is developmentally normal and appropriate and is why we give them chewable board books. It is not in any way an indication that the child is too young for a book!
- *12-month-olds* may point with 1 finger to indicate interest in a picture; parents should see this as developmental progress.
- *18-month-olds* may turn board book pages and may insist on turning back again and again to a favorite picture.
- *2-year-olds* may not sit still to listen to a whole book but will still enjoy looking at individual pages or having parents read them stories bit by bit.
- *3-year-olds* may retell familiar stories and may memorize their favorite book.
- *4- and 5-year-olds* may start to recognize letters or their sounds. They can understand and follow longer stories.
- *School-age children* will start to be able to read to you—but do not stop reading to them—and enjoy taking turns.

[a] Specific guidance can help parents with age-appropriate expectations for how their children will physically handle and interact with books, and respond to stories.

Adapted from Reach Out and Read. Milestones of early literacy development. www.reachoutandread.org/resources. Accessed February 19, 2020. Used with permission.

Primary Care Physicians Can Make a Difference

The primary care setting is the ideal venue for literacy promotion. Almost all parents will bring in their child for routine examinations or urgent visits, which provides an opportunity to reach a broad group, not just those seeking learning experiences for their children. In fact, 96% of all children younger than 6 years see their physician at least once annually. Each child is seen for multiple visits from a very young age, providing repeat opportunities to discuss reading aloud during the critical first years. Suggestions in support of literacy-focused activities are a logical extension of the advice about growth and development that parents are already receiving at these visits. Those who provide primary care can review daily activities in which reading aloud can be incorporated, such as reading traffic signs, store names, or simple food labels. When parents trust and value advice from their primary care physician, early literacy messages assume greater credibility.

The effectiveness of this primary care model to promote reading aloud to young children has been demonstrated in multiple research studies. Parents who received even 1 book were much more likely to read aloud to their children and report reading as a favorite activity of their child. The effect was greatest for the poorest families, which is an important finding for children who may need this intervention the most. The outcome was similar for non-English-speaking families, and the findings held even if the provided book was written in English. Finally, and most encouraging, toddlers and preschoolers who had received care in clinics in which the Reach Out and Read model was used had higher scores on language and vocabulary assessments than children who had not been not served by the program.

Medical professionals who promote literacy and use the Reach Out and Read model of providing books and advice will help build stronger bonds between health professional and family. Using clinic visits as an opportunity to tailor age-appropriate advice for parents and emphasize the importance of reading aloud and the beneficial effects is favorable for all.

CASE RESOLUTION

You speak to the mother about the benefits of reading aloud to her children. You give the 9-month-old a board book with pictures of baby faces. You demonstrate, showing how the 9-month-old is interested in the pictures and engages with vocalizations as you describe each page. At the end of the visit you also find a gently used rhyming book that the mother can take home for her 6-year-old daughter.

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CHAPTER 35

Gifted Children

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CASE STUDY

A 3-year-old girl is brought to your office for well-child care. Her parents believe that she may be gifted, because she is much more advanced than her sister was at the same age. The parents report that their younger daughter walked at 11 months of age and was speaking in 2-word sentences by 18 months. She is very "verbal," has a precocious vocabulary, and constantly asks difficult questions such as, "How do voices come over a radio?" The girl stays at home with her mother during the day but recently began attending a preschool program 2 mornings a week. She enjoys preschool and plays well with children her own age. She also likes to play with her sister's friends from school.

The girl is engaging and talkative. She asks questions about what you are doing during the examination and demonstrates impressive knowledge of anatomy. The physical examination is normal.

Questions

1. How are gifted children identified?
2. What characteristics are associated with giftedness?
3. What are the best approaches for optimizing the education of gifted children?
4. What is the role of the pediatrician in the care of gifted children?

Addressing caregiver concerns about giftedness provides an exciting intersection of strengths-based pediatric medicine with the educational system. Because several definitions of giftedness exist, prevalence rates vary. Identification of gifted children coupled with advocacy can promote an optimal educational match for the child; however, identification systems currently in use may result in an underrepresentation of children from socioeconomically disadvantaged backgrounds. Pediatricians can help counsel families in the creation of a supportive environment for their children and can advocate on behalf of children and families within the educational system.

Giftedness has been defined in several ways. The psychometric definition of giftedness is based on scores obtained on standardized intelligence tests. The 2 most frequently used cutoff points are 2 standard deviations above the mean (intelligence quotient [IQ] of 130–135) and 3 standard deviations above the mean (IQ of 145–150). Children with these scores are in the upper 2% and 0.1% of the IQ distribution, respectively. Intelligence quotient, which is considered to be fairly stable after 3 or 4 years of age, is the best single predictor of scholastic achievement at all levels, from elementary school through college.

A second definition of giftedness is based on real-life achievements or performance of exceptional skills rather than test scores. Children with special talents (other than general intelligence) in areas such as music, mathematics, ice skating, chess, or drama fit this description. Other definitions of giftedness recognize motivation, commitment, perseverance, high self-esteem, and creativity as personality traits that allow children with above-average ability to develop exceptional talents. This collective group of traits is often referred to as the "potential to achieve" academic or other success.

Epidemiology

The prevalence of giftedness depends on the somewhat arbitrary definitions of giftedness and the varied approaches to the identification of gifted children. Traditional screening systems identify 3% to 5% of students for participation in gifted programs in schools. Some schools use an alternative system in which 10% to 15% of children are recognized as above average. With the goal of fostering giftedness in these children, schools offer them enriched programs.

Intellectual giftedness in children has been associated with the social, economic, and educational background of their families. Factors that correlate with higher IQ scores in children are more years of parental education, higher IQ scores of mothers, increased family income, smaller family size, and longer intervals between siblings. Children from low-income and minority backgrounds are less likely to be identified as gifted than other children. Black, Hispanic, and Native American students are underrepresented by 30% to 70% in gifted programs in the United States. In particular, when single intelligence testing is used to identify gifted children, students from diverse cultural backgrounds are more likely to be excluded from programming opportunities. Some studies have also found that teacher referral–based systems may be more likely to underidentify students from diverse backgrounds if most of the teachers have cultural or ethnic discordance with the student.

Although research indicates that, as a group, children who are academically gifted begin to walk, verbalize, and read earlier, this area of research is still in its infancy, and conflicting results have been reported. Thus, these factors are not useful for predicting giftedness in individual children.

Evaluation

One of the primary goals of child health promotion is developmental monitoring. The early identification of developmental delays, which allows for prompt intervention, is among the primary purposes of such monitoring. Techniques for developmental assessment include review of developmental milestones with parents and discussion of parental concerns, informal observation of children in the office, and formal screening with standardized tests, such as the Ages and Stages Questionnaires.

Identification of Gifted Children

Although parents' first concern is usually to confirm that their child is developing normally, it is not uncommon for parents to ask if their child is gifted. Such questions are typically motivated by parents' desire to optimally encourage their child's development. Sharing information and observations with parents during developmental monitoring may facilitate parent-child interaction and child development. In a competitive society, the pediatrician should look for signs that above-average abilities are the result of undue pressures placed on children, such as incessant teaching or overscheduling of time.

Infancy and early childhood may not be the best time to determine whether a child is gifted. Age of attainment of developmental milestones and performance on standardized tests (eg, *Bayley Scales of Infant and Toddler Development*) during the first 2 years after birth are unreliable predictors of intellectual giftedness. Reasons for this lack of reliability may include weaknesses in the tests and variable rates of child development that result in transient precocity or delay. Tests that focus on visual memory tasks in infants may be better predictors of later academic intelligence, although additional research is required on the efficacy of such tests. Additionally, many special talents that comprise giftedness, such as creativity or artistic or musical ability, may not manifest until children are older.

The determination of giftedness in older children may involve several factors (Box 35.1). The early identification of giftedness allows for the development of an appropriate educational program that is optimally matched to a particular child's ability to learn. Without early identification and intervention, children who are intellectually gifted may become disillusioned with school, lose interest in learning, fail to develop study skills because they are never challenged to think and work hard, and develop a pattern of underachievement that may be difficult to reverse by the middle grades.

Box 35.1. Factors Used in the Identification of Giftedness in Children

- Intelligence tests
- Standardized achievement tests
- Grades
- Classroom observations
- Parent and teacher rating scales
- Evaluation of creative work in a specific field (eg, poems, drawings, science projects)

Special Groups of Gifted Children

Giftedness is harder to identify in some children. In the child with physical disability, giftedness is often obscured by the obvious physical disability, which demands attention. Such children may participate in special programs in which their physical needs are the major concern, to the detriment of their academic or artistic potential. In addition, poor self-esteem associated with the disability may prevent these children from realizing their potential. To identify giftedness in the child with physical disability, parents and teachers must make a concerted effort to search for potential and encourage its development. Strengthening a child's capacities may involve training in the use of a wheelchair or computer or taking frequent breaks to prevent fatigue.

Giftedness also commonly goes unnoticed in children with learning disabilities. Exceptional and poor abilities can coexist in a child. In fact, an estimated 10% of gifted children have a reading problem, reading 2 or more years below grade level. Albert Einstein, Auguste Rodin, and John D. Rockefeller are famous examples of brilliant individuals who had challenges with reading and writing. An extreme example of the occurrence of extraordinary and deficient abilities together in 1 individual is the child savant. Affected children possess amazing abilities in 1 area (eg, music, drawing, mathematics, memory), but they exhibit delays in other respects. In addition, they have behavioral problems that resemble autism, such as repetitive behavior, little use of language, and social withdrawal. Learning disabilities may obscure children's talents, thus preventing fulfillment of their potential.

Conversely, children's giftedness may mask their weaknesses, depriving them of needed help. Worst of all, gifted children with learning disabilities may manage to barely "get by" in the regular classroom setting and fail to receive recognition for strengths or weaknesses. Large differences on intelligence and achievement tests between scores in different areas, such as language and spatial abilities, may indicate both giftedness and a learning disability. Research suggests that programs that focus on strengths, not deficits, enhance self-esteem in gifted children with learning disabilities and can be extremely beneficial in their academic development.

The identification of giftedness is also difficult in children who underachieve. Parents may approach the pediatrician with the following frustrating problem: Their child is doing poorly at school, although they believe that the child is bright because of the child's abilities and participation in advanced activities at home. Underachievement may result from a learning disability; poor self-esteem; lack of motivation; or the absence of rewards, at home or at school, for succeeding in academics.

As previously stated, giftedness is less likely to be recognized in children from families of low income or who are ethnically diverse. For school districts that request privately obtained testing for entry into advanced educational programming, the costs may be prohibitive for some families. Additionally, many of the tests used to identify giftedness have been "normed" on white, English-speaking,

middle-class children. Furthermore, studies have shown that relying on referrals from teachers who have not had additional training on recognizing giftedness are likely to result in students who do not match typical cultural perceptions of the "gifted child" being overlooked. Students who are learning English as a second language are even more likely to be overlooked for placement into advanced educational programming. For new immigrant families, there may be different sociocultural expectations of behavior in school, cross-cultural stress, or symptoms such as posttraumatic stress or depression that may mask giftedness or academic potential. Validation of newer methods of assessment that are less fraught with cultural and socioeconomic bias is ongoing. Until validated tests are available that are sensitive to socioeconomic differences, a combination of other means of identifying giftedness should be stressed, such as assessment of creative work and teacher, student, and perhaps community nominations.

Management

At Home

Loving, responsive, stimulating parenting should be encouraged for all children, including those who are gifted. Parents of gifted children may feel inadequate, fearing that their child is smarter than they are. The pediatrician can provide parental reassurance by telling parents, "You must have been doing something right for your child to have been identified as gifted." Children's librarians, periodicals written for parents and teachers of gifted children (eg, *Gifted Child Today*), and the local chapter of the National Association for Gifted Children are good resources for parents.

Parents are often overwhelmed with complex questions from their precocious preschool-age children about issues ranging from homelessness and world hunger to theology and the creation of the universe. The pediatrician should tell parents that they should not be afraid to admit that they do not know all the answers and should work together with their child to find the answers.

The pediatrician may need to warn parents about putting too much pressure on their gifted children. For example, enrolling children in multiple classes often leaves little free time for unstructured play. Play affords many opportunities for self-learning, interaction with peers, and development of creativity and initiative. Parents of infants, toddlers, and preschoolers should be encouraged to take cues from their children. If children have a rich environment with plenty of objects and books to explore, diverse experiences, and stimulating interactions, they will develop their own interests. Other educational materials and special instruction can then be provided in a particular area of interest.

Children who are gifted are often mistakenly considered to fit the stereotype of troubled, socially awkward "nerds." With the exception of children at the genius extreme (IQ >180), gifted children are generally more sociable, well-liked, trustworthy, and emotionally stable than their peers, with lower rates of mental illness and delinquency. Nevertheless, they have the same emotional needs as other children. Gifted children may prefer to play with older children whose interests and abilities are closer to their own. This should be allowed as long as these relationships are healthy.

Parents should be encouraged to treat children who are gifted the same way they do their other children. For example, age-appropriate responsibilities and chores should be encouraged. Siblings of gifted children may become resentful if attention is centered on their gifted sibling. They may feel inferior, particularly if gifted children surpass them in school. Tensions may be magnified if gifted children become friends with their older siblings' friends. To preserve a sense of self-worth and competence in siblings, the pediatrician should recommend to parents that they set aside special time to spend with each of their children. Parents should encourage other talents (eg, musical abilities, athletic abilities) in siblings. Older siblings should receive the special privileges and responsibilities that come with age, such as staying up later or doing different chores. Any tensions within the family should be openly discussed and addressed.

At School

Parents often seek advice from their pediatrician about educational planning for children who are gifted. A learning environment with the optimal degree of challenge—hard enough to require new learning and stave off boredom, but not so hard as to be discouraging—is the goal for all children. Parents of young children should select a preschool with a flexible program and capable teachers to accommodate children with precocious skills. Parents of school-age children must decide whether *acceleration* (ie, starting school earlier or skipping grades) or *enrichment* (ie, staying in the same grade but supplementing the regular curriculum) is more appropriate (Table 35.1). The choice of approach is dependent on the particular child.

Table 35.1. Acceleration Versus Enrichment in Gifted Education

Strategy	*Advantages*	*Disadvantages*
Acceleration	May provide suitable academic challenge May have social benefits Can be offered by all schools Inexpensive	Difficult to reverse May have to skip more than 1 grade to be properly challenged
Enrichment	Classmates are the same age May expose children to subjects they would not otherwise learn Appropriate for children who are mildly gifted	May be expensive and inaccessible to many families because of tuition and transportation costs Inadequate for children who are highly gifted May isolate gifted from non-gifted children and encourage "elite" label Potential for excessive homework if children are required to make up the regular class work as well when they miss class to participate in an enrichment program

Parents and teachers of gifted children are usually concerned that children in accelerated programs may have problems with social adjustment if their classmates are older. Existing evidence suggests, however, that children who are gifted benefit socially from acceleration. Gifted children in accelerated programs participate in school activities (except contact sports) more often than gifted children placed with classmates of the same age. Even when children who are gifted are placed with children their own age, they tend to make friends with older children with whom they share more interests. Gifted children also make up any curricular content missed by grade skipping. Because the process may be difficult to reverse, acceleration may not be the best option if doubt exists whether doing so is in the child's best interest.

Enrichment involves keeping gifted children with same-age classmates but supplementing the regular curriculum. Regular class placement with a teacher who is willing to offer extra work (eg, special projects) in addition to grade-level assignments, part-time programs to supplement regular class work (eg, field trips, foreign language classes), honors classes that group bright children together for their basic curriculum, and independent study by the family at home are all examples of enrichment programs. These programs may work well for some children who are gifted, depending in large part on the resources and funding available and the experience, creativity, and enthusiasm of the teachers involved.

Some enrichment programs may isolate gifted from nongifted children, however, and encourage labeling of the gifted students as "elite." If children are required to make up the regular class work that they miss when they are involved in the enrichment program, they may find themselves overloaded with homework.

Often, a combination of acceleration and enrichment programs is the best option. Acceleration or enrichment alone may be inadequate for the brightest children. Acceleration may be insufficient for markedly advanced children who would have to skip 2 or 3 grades to be appropriately challenged. The pediatrician should recommend that parents work closely with teachers to achieve the best learning environment for their children. Some factors that should be considered are age, physical size, motor coordination, emotional maturity, personality, and particular areas and degrees of giftedness of the child. Acceleration may be a better option for a physically large, outgoing child than for a small one. Gifted children should be asked what they would like to do.

When evaluating the suitability of an educational situation for their gifted child, parents should watch for certain warning signs. Excessive homework should not be expected or tolerated, because it cuts into the child's time to play and develop socially. The emphasis in gifted education should be on broadening perspectives, not increasing busywork. If children who are gifted are developing a sense of elitism or peer animosity, the nature and philosophy of the program should be questioned. Boredom with schoolwork, not needing to study, signs of depression, or symptoms suggestive of school phobia, such as recurrent abdominal pain or headaches on school mornings, should prompt investigation into the suitability of the child's program.

Homeschooling, either part-time to complement classroom curricula or full-time, is an educational alternative. To decide if this is the best choice for the family and the child who is gifted, parents who are considering homeschooling are advised to gather as much information as possible, including talking to other parents who are homeschooling their children, reviewing sample curricular materials, and contacting school districts and state departments about requirements and specific steps.

Schools with students from low-income or minority backgrounds tend to use their limited resources to help students who are doing poorly in school, rather than gifted students. In addition, children from low-income or minority backgrounds may experience further barriers to academic achievement, including lack of informational materials about gifted programs in parents' native languages and difficulty meeting requirements because of parental employment responsibilities and lack of transportation. Research has shown that programs for gifted children from such backgrounds benefit all students by creating positive role models and promoting the school as a place for the cultivation of excellence. In addition to providing support for individual gifted children and their families, the pediatrician may choose to engage in an active advocacy role within the community by, for example, promoting diverse educational experiences for students of all backgrounds, helping policy makers discover and remove barriers to participation, and working with community organizations to educate families from minority or low-income backgrounds about educational opportunities for their children who are gifted.

Prognosis

Children who are gifted are a diverse group, comprising children with exceptional academic, artistic, or other abilities, combined with the creativity and commitment to achieve their potential. Children may be gifted in 1 area and average or even below average in another area. The purpose of identifying gifted children is to provide them with an educational environment to help maximize their potential. The pediatrician is poised to help children and their families recognize that other factors in addition to cognition, including social development, concepts of self-worth, self-discipline, and resilience, are also vitally important to the overall success and well-being of the child. Pediatricians can serve as a resource for parents in raising children who are gifted and helping children and families obtain appropriate evaluation, educational programs, and supportive resources. The prognosis for gifted children is excellent.

CASE RESOLUTION

The physician should reaffirm the parents' observations that their child is gifted. The parents should be encouraged to explore programs in which their daughter's talents may be fostered, but they also should be advised that even gifted children need time for play and unstructured activities.

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CHAPTER 36

Children and School: A Primer for the Practitioner

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CASE STUDY

An 8-year-old boy is brought in by his parents in early April because his third-grade teacher informed them that he is currently failing in school and may not be promoted to the fourth grade. Review of his medical, developmental, and school histories reveals that he was a colicky infant and continued to be difficult as a toddler. His language skills were somewhat delayed, although not enough to warrant a full evaluation. His preschool teacher felt that he was easily distracted when doing seat work. In kindergarten, he had some difficulty learning all his letters, numbers, and sounds. Early reading was difficult in kindergarten and first grade but improved by the end of the first-grade year. Second grade was fairly good, except for continued concerns about inattention and distractibility. By third grade he was struggling more, especially with writing, and not performing within grade level in several areas. He also continued to be inattentive and distractible in his classroom.

Examination reveals a well-developed and well-nourished boy whose growth parameters are within normal limits for his age. He appears somewhat anxious in the examination room, and when asked about school he tells you that he feels he is just not as smart as the other children in his class.

Questions

1. Should grade retention be considered when a child is failing in school?
2. What are the potential disadvantages of grade retention?
3. What are factors to consider when evaluating a child for school failure?
4. What steps should be taken at this time by the parents and the school for the boy in this case study?
5. How could early intervention have affected the boy's performance?

Pediatricians are the medical practitioners most knowledgeable of typical and atypical child development. Their routine contact with young children and their families, as well as their longitudinal perspective on their patients' lives, places pediatricians in a unique position to evaluate, diagnose, and manage not only children's medical needs but also their developmental, social-emotional, behavioral, and educational needs. Research has highlighted the importance of early experiences to optimize development and supported early intervention for children with developmental delays. Traditionally, the 5-year-old health maintenance visit has been regarded as the "school readiness" visit. However, waiting until this visit to address concerns or provide preventive guidance for educational readiness is too late. School readiness and the academic, behavioral, and social-emotional development it entails must be promoted from infancy through early childhood.

During the school-age years, pediatricians should continue to monitor children's educational progression by inquiring about academic, social-emotional, and behavioral development. Parents often turn to pediatricians for advice on their children's behavioral or academic difficulties at school. Early academic, behavioral, and social-emotional difficulties place children at risk for school disengagement and school failure. It is imperative that pediatricians have an understanding of the multiple facets, evaluation, and management of children's school readiness needs and the ways in which delays or deficits in academic, cognitive, physical, behavioral, and social-emotional development can affect a child's school engagement and long-term success. The evaluation and management of educational difficulties requires a multidisciplinary approach; however, the pediatrician should have a principal role in monitoring the critical elements supporting school readiness and providing ongoing guidance, support, and advocacy for patients and their families.

Epidemiology

Attempting to establish a set of determinants that result in successful learning or that place a child at risk for failure is an oversimplification of the complexities of school readiness, school engagement, and school failure. School readiness, school engagement, and school failure are nonlinear cumulative processes, not solitary events, and a multidisciplinary approach to assessment and management is required.

School readiness is the term used to describe those qualities and traits that are considered prerequisites for a child to be ready for

school success. When defining school readiness, parents tend to focus on the pre-academic skills their child has mastered (eg, identifying letters and sounds, counting, writing their name). Teachers' definitions of readiness regularly incorporate social skills and behavior as well. Factors identified in the literature as affecting school readiness include physical health, motor skill development, social and emotional development, language development, adaptive skills, and cognitive abilities. In addition, significant additional factors exist that readily affect school adjustment and success other than a child's skills and attributes, such as parent-child interactions, access to quality early childhood education, and both positive and negative life experiences (see Chapters 141 and 142).

Language deficiencies and problems with emotional maturity are cited most often as the factors that most restrict school readiness. Language development and school readiness are intertwined. Language proficiency provides a strong foundation for the cognitive and literacy skills required for school achievement. By providing a rich language environment from infancy, parents give children a head start on school success. Currently, however, more than 1 in 3 American children start kindergarten without the language skills necessary to learn to read. Similarly, with regard to emotional maturity, a recent study found that students who entered kindergarten lagging their peers in social-emotional skills were more likely to experience grade retention, receive special education services, and be suspended or expelled at least once by the fourth grade. *School engagement* can be broadly defined as meaningful student involvement throughout the learning environment. Research has shown that school engagement is associated with positive outcomes, including academic achievement and persistence, that is, staying in school until graduation. Within the school research literature, school engagement has 3 components: behavioral, emotional, and cognitive. *Behavioral engagement* is related to active participation, both in the classroom and the school community as a whole. It includes following classroom norms; demonstrating good conduct; and being involved in academic, social, and/or extracurricular activities. *Emotional engagement* refers to students' emotional reactions to teachers, peers, academics, and the school as a whole. Emotional engagement creates a sense of belonging and value to the school community. *Cognitive engagement* is related to students' investment in learning. It encompasses the problem-solving flexibility and coping skills students use as well as the hard work they do to understand and master the curriculum presented to them. School engagement is considered crucial to achieving positive academic outcomes and protecting students from school failure.

School failure is a multifaceted, epidemiologically complex issue. Research suggests that health and educational success are intricately connected. Compared with non-affected children, children with physical illnesses, mental health concerns, socio-emotional concerns, behavioral issues, and neurologic deficits are more likely to have difficulty learning throughout their school careers. They are at increased risk of poor attendance, poor achievement, academic decline, and failure to graduate from high school. Dropping out of school, which is commonly seen as an event, is in fact a process that often begins with early school failure.

Overall, high school completion rates in the United States have been slowing rising over the last decade, with 83% of all students graduating from high school. Graduation rates vary by state, however, and are lower for children from low-income families and for children with disabilities. The overall rate of high school completion is 76% for low-income students, with some states reporting rates as low as 63%. The high school completion rates for children with disabilities are even more concerning. In the United States, approximately 64% of students with disabilities graduate from high school, with rates as low as 29% for certain states.

Approximately 15% of children in the United States have a developmental disability. In the US public school population, 13% of children receive special education services under the Individuals with Disabilities Education Act (IDEA) of 2004. These services are provided to students with qualifying disabilities, if their disability affects their academic achievement or educational performance. Not all children with a diagnosed disability qualify for or require special education support (Box 36.1).

The number of children with diagnosed disabilities is significantly lower than the number of children who experience some level of adverse environmental, socioeconomic, or stress-inducing conditions that negatively affect their ability not only to get to school each day but be ready to learn on arrival (see Chapters 141 and 142). These children experience poor educational outcomes when they do not receive comprehensive support, intervention, and services. Youth who interface with the juvenile justice system have previously experienced increased rates of academic failure, disengagement from

Box 36.1. Special Education Eligibility Categories Under the Individuals with Disabilities Education Act of 2004 for Children and Youth Age 3 Through 21 Years[a]

- Autism
- Deafness
- Emotional disturbance
- Deaf-Blindness
- Hearing impairment
- Intellectual disability
- Multiple disabilities
- Other health impairment
- Orthopedic impairment
- Specific learning disability
- Speech or language impairment
- Traumatic brain injury
- Visual impairment, including blindness
- Developmental delays[b]

[a] To fully meet the definition and eligibility for special education and related services as a "child with a disability," a child's educational performance must be adversely affected as the result of 1 of the 14 categories listed here.

[b] The Individuals with Disabilities Education Act of 2004 allows each state to determine whether to use this eligibility category for student age 3 through 9 years.

school, and/or school disciplinary problems. More than half of such students perform academically below grade level. This population meets eligibility for special education services at 3 to 7 times the rate of their nonincarcerated peers. Approximately 85% of incarcerated juveniles are functionally illiterate (ie, lacking the literacy skills to manage daily living and employment tasks that require reading) or low literate. High school dropouts are 3.5 times more likely than high school graduates to be arrested in their lifetime and 63% more likely to be incarcerated than their peers with 4-year college degrees.

Research has not supported retention as an effective remediation strategy for poor school performance, and many studies have linked retention to future school failure. Grade retention rates in the United States have declined in the past decade, and currently, approximately 10% of students are retained each school year. Most retentions occur in kindergarten, with retention rates between 1st and 12th grade of 3% to 5%. However, retention rates as high as almost 9% in these grades have been reported for students of color, students of parents without a high school diploma, students whose families receive public assistance, and students living in the Southern states. Children receiving special education services experience retention at a significantly higher rate, with 32% being retained at some point in their school career.

Considering that the average child in the United States spends approximately 50% of the waking day in a school or a similar learning situation for approximately 12 or 13 years, it follows that a lack of success in these settings will lead to difficulties for much, or all, of adult life. School difficulties that go undetected, untreated, and undertreated can result in establishing a lifelong pattern of frustration and failure. For example, children with attention-deficit/hyperactivity disorder (ADHD) are 2 to 3 times more likely to drop out of high school than their peers without ADHD, and those who attend college are less likely to graduate than their peers without ADHD (see Chapter 133).

Clinical Presentation

Defining school readiness is not an easy task, because the intellectual, physical, social, and emotional development among children of kindergarten age varies tremendously. To confound the concept of readiness, kindergarten expectations and standards have changed significantly in the past 2 decades, becoming less socially play based and more academically focused. School readiness involves far more than adequate pre-academic skills (Box 36.2). Early childhood educators also emphasize the importance of sufficient physical, cognitive, language, social-emotional, and behavioral skills to children's success in the formal schooling environment. Current research emphasizes the importance of children's "learning to learn behaviors," highlighting the role that abilities such as sustained attention, engaging in goal-directed tasks, impulse control, and emotional regulation have on children's engagement in learning activities and academic achievement. Children who can control impulses, consider options, and demonstrate flexible thinking and creativity are better able to actively engage in learning opportunities than their peers who lack those skills. As conceptualized by the National Education Goals Panel, school readiness encompasses 5 dimensions: physical well-being and motor development; social and emotional development; approaches to learning; language development (including early literacy); and cognition and general knowledge.

Lack of specificity of children's presenting signs and symptoms and of parental concerns make it challenging to determine a specific etiology for school failure. For example, parental concern about a child's inability to focus may be suggestive of an attention disorder, a learning disability, a mood disorder, or perhaps all 3. Parental concerns can be categorized into 3 broad areas: learning (eg, learning disability; problems with higher-order cognition, including intellectual disability), attention (eg, ADHD), and emotional/behavioral (eg, anxiety, depression, serious emotional disturbance). Signs of school difficulties are presented in Box 36.3. It is important to look not only at academic skills but also at other components of the educational experience, such as social and emotional experiences. Additionally, it is important to ascertain the basis for the perception that a child is failing. It is necessary to determine whether the problem exists in the eyes of the student, parent, teachers, or everyone involved. Academic achievement across subjects must be assessed, especially in the areas of reading, mathematics, and writing. It is also important to evaluate students with good skills who fail to perform satisfactorily in the areas of writing, planning, organization, project completion, test taking, or classroom participation. Difficulty with academic performance may result in school failure despite satisfactory academic skills. In addition to academic skills and performance, the development of good social skills and peer relations is equally important. Some students have difficulties "fitting in," which results in a disappointing educational experience despite academic excellence.

Pathophysiology

Developmentally, support exists for promoting school readiness from a young age. Research highlights the effect of nurturing relationships and positive experiences on early brain development. Strong neural connections are created and modified by positive reciprocal interactions, creating a solid foundation for learning. Conversely, adverse environments can have harmful effects on healthy brain development.

The developing brain continues to make new synaptic connections and discard underused connections from birth to approximately age 5 years, well before formal schooling begins. For example, it is known that children who grow up without being read to and with little exposure to books or printed language during their first 5 years are at increased risk for developing reading failure and subsequent school failure (see Chapter 34). School readiness must be promoted from infancy throughout early childhood; waiting for the 4- to 5-year-old well visit to address school readiness is too late. Most children with learning disorders experience language, motor skills, and emotional or behavioral problems well before they encounter difficulties in the classroom. These deficits are noted by parents an average of 3 years before the disability is formally identified.

Box 36.2. Questions Related to General School Readiness and The Five Domains of School Readiness

General Readiness Questions

- Have they had any preschool or group child care experience, and how did they respond in these settings?
- Were any behavioral, developmental, or emotional concerns raised during those group care experiences?
- Have they been screened for developmental delays, and have any delays been addressed?

Self-regulation and Social-emotional Readiness[a]

- Are they able to both express and control their thoughts, feelings, and emotions?
- Are they able to understand that others have thoughts, feelings, and emotions that are different from their own, and can they express empathy or compassion?
- Can they take turns, share, and cooperate with others?
- Can they share and play with other children?
- Do they play well with age-appropriate peers, or do they seem to consistently prefer to play with younger or older children or adults?
- Can they self-soothe or are they easily calmed down when they are upset or frustrated?
- Are they able to separate from parents for several hours?

Physical Health and Motor Readiness[b]

- Do they come to school physically ready to learn (eg, well nourished, adequate sleep)?
- Are their vaccines current?
- Have vision and hearing been evaluated?
- Do they demonstrate developmentally appropriate fine motor skills (eg, can they manipulate a crayon/pencil with a correct grasp, turn pages 1 at a time in a book, or print some letters and numbers)?
- Do they demonstrate developmentally appropriate gross motor skills, such as balance on 1 foot, hop, or skip?

Language and Communication Readiness[c]

- Are articulation errors developmentally appropriate?
- Is speech understandable to strangers?
- Can they hold a back-and-forth conversation about everyday topics of interest?
- Do they use correct sentence structure and speak in complete sentences?
- Do they use appropriate tenses/pronouns?
- Can children use language to express their thoughts and feelings or to follow simple oral instructions?
- Do they use age-appropriate vocabulary?
- Do they have beginning literacy skills, such as basic book concepts, print awareness, and story sense?

Cognitive Readiness[d]

- Do they have general knowledge, such as reciting the alphabet and rote counting, colors, days of the week, letters and numbers names, and basic shapes?
- Do they have more complex understanding, such as letter-sound associations, spatial relations, number concepts, and 1-to-1 correspondence?
- Are they able to solve problems, follow the logic in a story, think, and make decisions?

Approaches to Learning[e]

- Are they able to focus and sustain attention for a developmentally appropriate amount of time?
- Are they able to work in a group, with a partner, and independently?
- Are they able to control their emotions and persist at challenging tasks?
- Do they demonstrate curiosity and enthusiasm for learning?
- Can they tend to basic needs independently, such as toileting, washing hands, and asking for help?

[a] This domain focuses on children's social and emotional development, including their interpersonal and intrapersonal skills.

[b] This domain covers such factors as health status, growth, and disabilities.

[c] This domain focuses on expressive and receptive language skills and literacy development.

[d] This domain includes general knowledge as well as gaining knowledge by making connections with objects, events, or people for similarities, differences, and associations. It also includes knowledge about societal conventions.

[e] This domain refers to the ability to use skills to actively engage in learning.

Adapted with permission from National Education Goals Panel. Ready schools. Washington, DC: U.S. Government Printing Office; 1998

Another critical period in brain development occurs during adolescence, when the brain again undergoes a process of synaptic pruning and myelination that is especially notable in the prefrontal lobe, the area responsible for the *executive function skills* of reasoning, impulse control, attention, and planning. These skills are higher-order cognitive tasks that enable attention, self-regulation, planning, organization, and completion of goal-oriented tasks, all of which are necessary to effectively engage in learning.

Interventions designed to improve children's school connectedness and prevent later academic problems are most effective when

Box 36.3. Factors Related to School Difficulties That May Result in School Failure[a]

Intrinsic

- Not able to follow directions, pay attention, or finish a task
- Not able to carry thoughts or ideas to paper
- Not able to read, write, or spell appropriate to age and educational level
- Requires excessive time to complete homework/excessive parental involvement with homework
- Previously tested but not eligible for special education (eg, child may be a "slow learner")
- Hates school/psychosomatic symptoms
- Has few, if any, friends or change of friends
- Sudden change in behavior
- Low cognitive skills (ie, intellect)
- Specific learning disabilities
- Attention-deficit/hyperactivity disorder
- Speech and language disorders
- Mood and anxiety disorders
- Low self-esteem, self-concept, and self-determination
- Social-emotional difficulties
- Neurodevelopmental delays
- Motor coordination disorders
- Chronic or serious medical illness (eg, seizure disorder, cystic fibrosis, asthma)
- Vision, hearing, or speech difficulties
- Poor nutrition
- Sleep problems
- Substance use/abuse
- Genetic history (eg, family history of school problems)

Extrinsic

- Serious psychosocial concerns (eg, parental depression, history of abuse or neglect)
- Disruption in the family (eg, many moves, divorce, death)
- Poor school readiness/absence of enrichment prior to school entry (eg, early literacy exposure)
- Parental or school expectations not commensurate with child's abilities
- School and/or classroom placement (poor "fit" or poor instruction)
- Grade retention
- Poor attendance, missed instruction
- Multiple school changes
- Language/cultural differences
- Adverse childhood experiences

[a] School failure is not a single event or a linear process. This list provides examples of factors within individual children and their environments, whether home or school, that could place them at increased risk for school difficulties and failure.

they are provided during the preschool years, before a child enters formal K-12 schooling. *School engagement* stems from learning theories demonstrating that learning improves when students are curious, interested, or energized by their schooling and that learning worsens when students are bored, indifferent, or disengaged from their school. Levels of student engagement can be seen on a spectrum from deeply engaged to resistant. For students with fluctuating engagement or true resistance to participation in school and learning activities, a multitiered system of support (MTSS) is often needed to improve student outcomes. School engagement is adaptable and is a function of not only the child but the context, that is, the school environment. This implies that behavioral, emotional, and cognitive engagement can be responsive to prevention and intervention.

School failure has a variety of causes. Both intrinsic (ie, child-related) and extrinsic (ie, environmental-related) causes relating to the home or school environment must be considered (Box 36.3). In most cases, school failure is the result of a complex interaction between child, family, and school-related variables rather than the result of a single factor (eg, ADHD). When evaluating for the etiology of learning disorders, medical problems should always be considered. Neurologic, psychological, social-emotional, and behavioral disorders based in the central nervous system may also be responsible for school failure. Unrecognized disorders may be causes of school failure. For example, children with ADHD often have significant academic underachievement, poor academic performance, and poor educational outcomes.

Learning disorders are a broad group of neurodevelopmental disorders affecting children's ability to learn, such as speech and language impairments, intellectual disability, specific learning disabilities, and ADHD. Learning disorders are among the most frequently diagnosed developmental disorders in childhood.

Learning disabilities comprise a subset of learning disorders and are neurologically based processing problems that interfere with learning basic skills, such as reading, writing, and/or math, as well as more complex skills, such as organization, planning, abstract reasoning, short- and long-term memory, and attention. Learning disabilities are the most common learning disorder. Approximately 10% to 15% of children have learning disabilities, and reading disabilities are the most common type. Children with learning disabilities are the largest group of students receiving special education services in schools; these disabilities vary in degree, nature, and complexity.

A formal definition of specific learning disability was first outlined in federal law in 1975 as part of the Education for All Handicapped Children Act, now the IDEA. A *specific learning disability* is "a disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, that may manifest itself in the imperfect ability to listen, think, speak, read, write, spell, or to do mathematical calculations." The IDEA of 2004 expanded educators' options for determining whether a child has a learning disability by removing the requirement for use of a discrepancy model that identifies a learning disability as a significant difference between a child's intellectual ability (ie, intelligence quotient [IQ]) and academic achievement. That now-removed requirement was often called the "waiting to fail" model, because parents and schools had to wait until individual children's achievement fell significantly below their ability level before a learning disability could be identified. Currently, children can be identified with a learning disability if they do not exhibit adequate achievement when provided with age- or grade-appropriate learning experiences; do not make progress sufficient to meet age- or grade-level standards when provided research-based intervention (ie, response to intervention); or do exhibit a pattern of strengths and weaknesses in academic performance, achievement, or both, relative

to grade-level standards, or intellectual development. Specific learning disabilities do not include "learning problems that are primarily the result of visual, hearing, or motor disabilities; intellectual developmental disorders; of emotional disturbance; or of environmental, cultural, or economic disadvantage."

The criteria of learning disorders are listed in Box 36.4. For a more comprehensive list of diagnostic criteria and coding information, refer to *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*). Similar to IDEA, *DSM-5* removed the discrepancy between IQ and the affected learning area as a requirement for diagnosis. This change is based on research showing that children who meet and those who do not meet the IQ-discrepancy criterion do not differ in terms of symptomatology, underlying cognitive deficits, or response to effective intervention.

Although it is difficult to do, it is important to differentiate students with neurologically based learning problems from those with learning problems caused by other factors. For example, a student's disability may predispose the individual to learning problems even in highly accommodating environments, whereas inadequate environments can result in significant learning problems even in the absence of disability. This differentiation is vital to management or intervention success. An inadequate environment or a student disability are best addressed with evidence-based instruction in the deficit areas; focusing only on addressing the academic deficit will not alleviate comorbid negative social-emotional, behavioral, or environmental conditions. Before evaluating for child-related pathology or underlying dysfunction, such as specific learning disabilities, cognitive delays, language disorders, or mental health disorders, the physician should investigate external situations that may be causing or exacerbating the problem (eg, underperforming schools, lack of parental involvement, poor student-teacher relationship, mismatch between a child's ability/disability and the learning environment).

Evaluation

History

A thorough history is necessary to help the pediatrician assess a child's strengths and challenges and formulate a hypothesis for diagnosis. Research on prevention, resiliency, and social-emotional development demonstrates that the presence of assets or strengths is positively linked with improved outcomes in all domains of development. Incorporating educational and learning strengths assessment in the primary care setting can facilitate discussion of positive changes and prevention and can make the discussion of challenges and intervention more comfortable for parents and children.

Box 36.4. Criteria for Specific Learning Disorder

- Difficulties learning and using academic skills: word reading; meaning of what is read; spelling; written expression; number sense, facts, or calculation; mathematical reasoning
- Academic skills below expected for chronological age; interferes with academic/occupational performance/activities of daily living
- Learning difficulties begin during school-age years or when academic demands exceed the patient's capacities
- Learning difficulties are not secondary to intellectual, visual, auditory, mental, or neurological disorders

Derived from *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.

School Readiness

Historically, pediatricians assessed school readiness during the 5-year-old health maintenance visit, but currently it is understood that the optimization of development and school readiness should be addressed beginning in infancy. The American Academy of Pediatrics (AAP) has highlighted 5 domains of school readiness, which are consistent with the 5 dimensions of school readiness from the National Education Goals Panel. These domains include self-regulation and social-emotional readiness, physical health and motor readiness, language and communication readiness, cognitive readiness, and approaches to learning (Box 36.2). The physician should interview the parent and observe the child to assess the acquisition or progression toward these readiness skills. Mastery of these skills is not necessary for social and academic competence and should never be used as exclusion criteria for a child beginning formal schooling, because public school kindergarten classrooms and curricula are designed to accommodate a diversity of skill levels. Providing this information to families early in a child's development can help families make decisions about early childhood programs and, if necessary, early interventions. More than 50% of children younger than 5 years regularly attend some type of child care or preschool program; thus, including questions about the quality and experiences within these settings is an important part of the history.

School Engagement/School Failure

When evaluating for school engagement and/or school failure, the physician should elicit information from parents, teachers, and the children themselves (Box 36.5). A review of present and past report cards provides information not only on academic progress relative to the grade level standards but also on the child's behavioral, social-emotional, and classroom adaptive skills. Teacher behavior rating forms, school district and state academic evaluations, and results of any school-based psychoeducational evaluations also should be reviewed.

Box 36.5. What to Ask

School Engagement and/or School Failure

- Have the child tell you about experience at school. What classes or subjects does the child like or dislike and why? Does the child have friends? Does the child participate in any extracurricular activities?
- Have any behavioral, social, emotional, or attentional concerns been raised by the child or the classroom teacher?
- How is the child's academic achievement? Is the child having problems in all academic areas, or are particular subjects especially difficult whereas others are not?
- Do concerns exist about educational performance, such as test taking, project organization, or homework completion?
- Are there attendance issues? How many days of school has the child missed?
- Has any testing (eg, psychoeducational evaluation) been performed by the school district or privately?
- Is the child receiving any accommodations or special services (eg, intervention group, counseling, speech therapy) at school?

Clinical approaches to early identification of children at risk for school failure include risk assessments and developmental surveillance and screening. Children from economically disadvantaged backgrounds are at the highest risk for problems in school. Developmental surveillance and screening allow pediatricians to identify children with developmental, behavioral, and emotional delays and to provide appropriate guidance, as well as referral to early intervention programs (see Chapter 32). Historical factors associated with an increased risk of school-related problems include preterm birth, low birth weight, small for gestational age, and maternal history of tobacco, alcohol, or illicit substance use during pregnancy. Developmental risk factors include delays in the acquisition of skills, especially those involving language. Medical factors that may affect school readiness include lead poisoning, iron deficiency anemia, and failure to thrive. The presence of chronic medical conditions (eg, asthma, diabetes mellitus, seizure disorders) can also affect school performance directly or indirectly via absenteeism, medication effects, or self-esteem issues. Environmental risk factors include poverty and lower socioeconomic status, parental mental health issues, domestic violence, substance abuse, or a family history of school problems or learning disabilities.

Physical Examination

In terms of school readiness, the most important aspect of the 5-year-old health maintenance physical examination includes careful assessment of hearing, vision, speech, and language. Fine and gross motor skills, attention and listening skills, ability to follow rules and directions, social skills, and self-help skills (eg, asking for help when needed, independently using the restroom and washing hands) also should be assessed.

The physical examination has a limited but important role in the evaluation of school failure. Signs of short attention span, distractibility, overactivity, sadness, or anxiety all should be noted. Special attention should be paid to head circumference, minor congenital anomalies, abnormal facies, and skin lesions suggestive of neurocutaneous disorders (eg, multiple café au lait spots, ash leaf macules). The pediatrician should evaluate the child's vision, hearing, and speech and language and conduct any other appropriate evaluations as suggested by the history.

Neurodevelopmental Assessment

School readiness assessment begins with routine pediatric surveillance and screening (see Chapter 32). Several brief school readiness tests have been developed for use by pediatricians (eg, Pediatric Examination of Educational Readiness). However, because the reliability and ability of such tests to detect subtle learning disabilities or arrive at more complicated diagnoses has not been established, it is difficult to recommend any of them for routine use. If a specific school readiness evaluation is warranted, it is best to make a referral to the school district or an independent specialist (eg, developmental and behavioral pediatrician, educational psychologist) for a full evaluation.

Neurodevelopmental assessment can help identify the etiology of school failure. *Neurodevelopmental assessment* surveys a child's abilities across the different areas of development (ie, fine motor, language, visual-spatial, memory skills) and helps identify areas of strength and weakness. Such an assessment can be performed by a professional such as a developmental and behavioral pediatrician or a psychologist. Psychoeducational assessment is also critical in the evaluation of children with school failure. Such an assessment includes an evaluation of cognitive abilities, academic achievement across subjects (eg, reading, writing, mathematics), perceptual processing strengths and weaknesses, social and emotional functioning, and the way in which these areas affect a child's learning. This can be accomplished through the public school system via the Individualized Education Program (IEP) process, as mandated by federal law (ie, IDEA) or privately, by an educational psychologist.

Management

According to the AAP policy statement "The Pediatrician's Role in Optimizing School Readiness," helping children develop the physical, social-emotional, cognitive, adaptive, and language skills needed to learn should begin at birth. Pediatricians can create a medical home in which they provide for children's physical health while also working with families to address developmental, social, emotional, and behavioral components of school readiness. Empowering parents with knowledge can give them the confidence to interact positively with their children's schools and allow them to effectively advocate for their children's educational needs.

Often, an important role in management is facilitating open communication about a child's needs. Pediatricians must acknowledge the emotions and fear that often are associated with discussing a child's delays or disability and must demystify the process of accessing support, interventions, and treatment. For both parents and children, the process of demystification can include assurances that all people have strengths and challenges and that resources and support are available. It is important to use an optimistic tone in such discussions. In addition to addressing the needs of families and children, the physician can also serve an important advisory role for the school on the educational implications of chronic medical conditions and the potential academic, behavioral, and social-emotional effect of a child's disability (eg, side effects of medications, appropriate seizure or allergic reaction responses).

Early intervention is the key to success in children's school readiness. Pediatricians are in the most opportune role to help families recognize the importance of early brain and child development and how they are affected by a child's environment and experiences. Teaching parents that their child's learning begins at birth and occurs in all environments not only can support children in meeting developmental milestones but can help them successfully acquire the curiosity, emotional regulation, and problem-solving skills they will need when they begin school. It is important for pediatricians to promote community and home activities to enhance readiness skills, refer families to community resources, and support access to early childhood programs.

During routine well-child visits, the pediatrician should ask families what child care arrangements they have made for their children and educate them about the importance of high-quality child care. To maximize quality early learning experiences, pediatricians can provide resources through links such as AAP's *Quality Early*

Education and Child Care from Birth to Kindergarten. For many at-risk children, early childhood education programs such as Head Start and other preschool compensatory programs may come too late. Early intervention programs for younger children and their families that promote good parenting, language stimulation, and learning through play are valuable and available in many communities.

Reading aloud to children is among the most important parent-child interactions physicians can promote, and it builds the child's skills required for eventual success in reading (see Chapter 34). Reading promotes language mastery, which is critical to school readiness.

Children who are at increased risk for school readiness problems because of medical, social-emotional, behavioral, or environmental concerns should be monitored carefully. If these children do not appear to demonstrate age-appropriate skills, they should be referred for further evaluation. Despite early intervention, some children still may lack age-appropriate school readiness skills. Options for these children include delayed school entry or enrollment in special educational programs. Delaying school entry may not be the best solution if children remain in the same environment that failed to produce readiness in the first place. In addition, studies have shown that students who are older than their classmates because of delayed school entry have increased rates of behavior problems, substance abuse, and other health risk behaviors in adolescence. Instead, it may be best for these children to enter school along with their same-age peers and, if necessary, receive school-based support to address any difficulties.

The management of school failure requires a multidisciplinary approach. Information from the school, including school reports, teacher conferences and notes, testing that has been completed, and input from other school officials, if appropriate, should be requested. The primary care physician can assist the child and family in working with the school system to obtain appropriate services. The primary care physician may also refer the child to appropriate resources in the community (eg, educational psychologist, developmental and behavioral pediatrician). Not infrequently, external factors such as social, family, and school-based issues may be difficult to alter. Knowledge of the educational laws and community services, as well as ongoing developmental surveillance and screening by the primary care physician, are necessary to help prevent school failure.

Grade retention is often suggested as an intervention for school failure. However, disparities exist in rates of grade retention based on sex, race/ethnicity, geographic locale, and socioeconomic circumstances. Boys, minorities, children born outside the United States, and children from homes led by adults with lower levels of education are retained at the highest rates. Although grade retention has been a common educational practice in US schools, overall retention rates have decreased notably in the past 10 years. Nonetheless, parents and school personnel may consider retention as a viable intervention option for children who are struggling for academic, behavioral, or social-emotional reasons. Research does not support retention as an effective remediation strategy, however.

Data suggest that grade retention has an adverse effect on most students. In fact, grade retention can diminish the positive outcomes of early intervention programs and is a significant contributing factor to school disengagement. Retention is the number 1 predictor of student attrition. Retained students, regardless of race, socioeconomic status, attendance, English language status, or parental involvement, are more likely to drop out of school than similarly low-achieving students who were promoted to the next grade level. Many teachers report suggesting retention to allow a child to "mature" or "give the gift of time," although minimal evidence exists that it is beneficial to repeat a grade without making changes to the curriculum or environment, or directly addressing the reason for retention. Educational alternatives to retention include directly addressing the reason retention was considered. For academic delays, extra support can be implemented in the form of targeted academic interventions, differentiated instruction, classroom accommodations, and, in some cases, special education services. Equally as important as remediating the areas of weakness is recognizing the child's areas of strength (eg, the idea of using children's strengths to leverage their weaknesses).

The pediatrician can assist families with children who are demonstrating learning, behavioral, and/or social-emotional difficulties that are affecting their academic achievement and performance. Public school systems, as mandated by federal and state laws, have systems of support and services available for students through both general and special education. Pediatricians' awareness and understanding of these systems is an important part of management, because they are often the first professional to be made aware of these delays.

The Every Student Succeeds Act signed into federal law in 2015 is a reauthorization of the Elementary and Secondary Education Act. The law includes a number of provisions to support success for all students by requiring districts and schools to establish a MTSS promoting children's academic, behavioral and social-emotional learning regardless of their ethnicity, socioeconomic status, primary language, family history, strengths, challenges, or disability. The MTSS is a schoolwide, data-driven, prevention-based framework for improving learning outcomes for all students through a layered continuum of evidence-based practices and systems. Common school prevention frameworks, such as response to intervention and Positive Behavior Interventions & Supports, are imbedded into MTSS. Within this tiered system is the recognition that providing every student the same level of supports, regardless of the quality, will not meet every child's needs. Levels of support are typically divided by the intensity of the services and the number of students they are designed to serve. Tier 1 includes foundational universal supports, which are evidenced-based practices that support the academic, behavioral, and social-emotional success of all students. Examples of tier 1 supports include training all teachers in differentiated instruction, implementing a school-wide positive behavioral system, conducting mental health screening of the entire student body, and adopting an evidence-based language arts curriculum. Supplemental and intensified services are designed for students who require more academic, behavioral, or social-emotional support, with the most intensive level of support targeted to students with the greatest needs. Examples of Tier 2 support for students who have been identified as having academic, behavioral, or social-emotional struggles may include homework modifications, small group reading intervention, or participation in a social skills

group. Students who have been identified as needing the most support may receive the most intensive interventions, such as 1-to-1 counseling or an individualized behavior support plan. Special education services are typically viewed to be tier 2 service.

Students with disabilities have the same right to public education as students without disabilities. To receive and benefit from that education, students with disabilities may need special education and/or related aids and services. Pediatricians can help parents of children with neurodevelopmental disabilities (eg, intellectual disability, mental health disorders, cerebral palsy, learning disorders, autism spectrum disorder) gain access to these services. Special education, as mandated by the IDEA, is not a place to which students with disabilities are sent. Rather, special education is a broad group of specially designed instruction, services, and supports that address the unique educational needs of students age 3 through 21 years who have a disability. In *specially designed instruction*, the content, methodology, or delivery of instruction is adapted to address the unique needs of a student with a disability. *Related services* are developmental, corrective, and other supportive services that are required to assist a child with a disability to benefit from special education. Examples of related services include transportation, speech and language therapy, occupational therapy, nursing services, and behavioral support services.

The IDEA requires public schools to provide free and appropriate education in the least restrictive environment for all children with a qualifying disability. That is, special education is provided at no cost to parents and includes services designed to meet the individualized educational needs of the students so they can access their educational program. Students with disabilities must also be educated with students without disabilities to the maximum extent appropriate. Special education services differ for each child, regardless of disability, because services, supports, and accommodations are individualized to meet each child's unique educational needs.

The IEP process begins when the parent requests an evaluation for special education services (Figure 36.1). A multidisciplinary

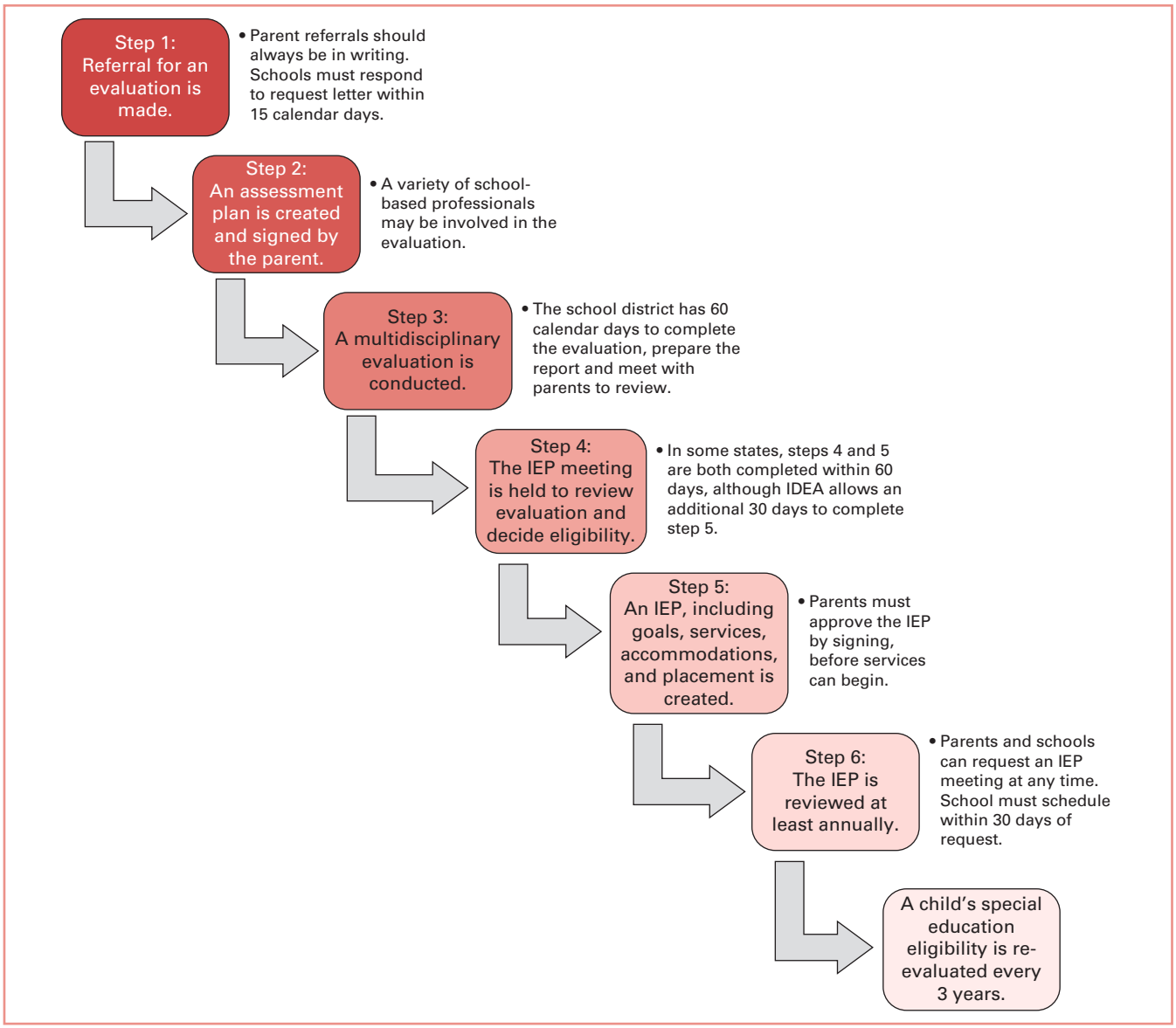

Figure 36.1. The Individualized Education Program process.

Abbreviations: IDEA, Individuals with Disabilities Education Act of 2004; IEP, Individualized Education Program.

evaluation designed to evaluate for special education eligibility and need is conducted. This evaluation may cover a broad range of areas depending on the referral concerns, including cognitive ability, academic achievement, social-emotional and behavioral functioning, adaptive behavior, language development, motor skills, and sensory processing. Eligibility for IDEA is dependent on meeting criteria for 1 of the 14 special education eligibility categories (Box 36.1). The IDEA and state educational codes provide operational definitions for these disability categories. It is important for the medical community to understand that educational systems do not use diagnostic criteria of the *DSM-5* or *International Classification of Diseases, Tenth Revision*. Rather, IDEA eligibility criteria use disability categories and focus on the ways in which a child's disability affects academic achievement or educational performance. A multidisciplinary team, including the child's parents, reviews and discusses evaluation results to decide on eligibility, identify educational needs, and create an IEP, including goals, services, accommodations, and placement. Should a child demonstrate behaviors that affect the child's or other students' learning, behavioral supports such as behavior goals or behavior intervention plans must be part of the IEP. The IEP is reviewed and revised regularly, with input from the IEP team members, including the parents and school-based professionals. A distinguishing component of IDEA is that the specific special education eligibility criteria used to qualify a child for special education services do not drive goals, services, and placement. Typically, within medical systems a child's diagnosis drives treatment; in the educational system, however, the child's unique educational needs, regardless of special education eligibility criteria, drive services. This is the individualized part of the IEP.

Special education services do have certain constraints. The purview of special education is the provision of educationally relevant services and supports. The purpose of special education is not to provide the full range of treatment options for a child with disability; rather, special education involves providing services and supports so that children with disabilities can gain access to and receive benefit from their education. For example, services such as occupational therapy and speech therapy need to relate to educational access and participation. Health professionals often view medical diagnoses and educational eligibility, as well as educationally related services and medically necessary services, as the same. They are not. Although these terms and services overlap, they are not interchangeable, and this can cause confusion and frustration for both medical providers and families. For example, a child with a medical diagnosis of autism spectrum disorder may not meet the special educational eligibility for a child with autism. However, this child may meet the educational eligibility for speech and language impairment and therefore would be eligible to receive special education supports and services to address the child's unique educational needs, regardless of the special education category in which the child was deemed to be eligible.

Section 504 of the Rehabilitation Act of 1973 (Section 504) is a civil rights statute that prohibits exclusion of individuals and discrimination against people with disabilities in federally funded programs and activities, including public schools and many after school programs. Students with a physical or neurologic impairment (eg, ADHD) that substantially restricts 1 or more major life activity are eligible for services under Section 504. Examples of school-based major life activities may include performing manual tasks, speaking, learning, working, thinking, and communicating. Students with disabilities who need only reasonable accommodations or modifications to be educationally successful within general education are frequently served under this law. The definition of disability and the way in which it affects a student at school is more broadly defined and has less stringent criteria in Section 504 than in the IDEA; thus, Section 504 provides for support and services for students with disabilities who do not require more comprehensive special education support.

The medical home concept of comprehensive, coordinated care is particularly useful for children with disabilities. Open communication among pediatricians, families, and schools can facilitate shared expertise and knowledge of the unique needs of children with special needs and can foster implementation of appropriate services to address those needs. Each state establishes its own special education code and regulations based on IDEA standards. Thus, pediatricians should be familiar with their state laws as well as the federal IDEA so that they can advocate for their patients at the time of school entry or whenever a child with a disability is not succeeding in school.

The pediatrician's role in advocacy on behalf of the child with a disability cannot be underestimated. Coordination of care, including educational services, for children and adolescents with chronic medical or disabling conditions should include the child's primary care physician. To effectively coordinate patient care, the pediatrician must be knowledgeable about federal and state education laws, establish linkages with early intervention services and parent support resources, and promote open communication with the child's family and school-based team. Additional examples of advocacy roles for physicians include involvement with assessment team processes at children's schools, consulting with local school districts, participation in local or state early intervention interagency councils, and serving as knowledgeable proponents for improved community and educational services.

Prognosis

Promotion of school readiness should be part of early pediatric visits. Children with daily exposure to reading, singing, and conversation have an enormous language and academic advantage over peers with fewer language and literacy experiences. Early literacy promotion through programs such as Reach Out and Read can educate parents about the importance of reading to their children and enhance children's exposure to early reading. Quality early childhood education programs also promote children's school readiness not only by introducing children to pre-academics but by introducing them to the social, emotional, and behavioral requirements for school success. Early academic success is the best predictor of later academic success. Children who begin school with the appropriate developmental skills, as well as family and community support, are prepared for learning. Pediatric primary care physicians

can serve an important role in improving educational and health outcomes for their patients by supporting coordinated care with children, families, and schools in the evaluation of and intervention for children who are not academically, socially, or behaviorally successful at school.

School failure results not from a single factor, but rather from a combination of risk factors. For children with neurologically based learning disorders or other neurodevelopmental disorders, the educational prognosis depends on the severity of the problems and the intensity and timing of the interventions the children receive. With coordinated support from educational, medical, family, and psychological sources, many of these students have successful school careers. Health impairments can contribute to school failure; however, social, behavioral, and emotional problems often contribute more significantly to academic difficulties. Students who may have endured major or chronic socioeconomic upheaval or environmental or familial trauma often continue to struggle unless they receive comprehensive changes in their support system.

The US Department of Education set a goal of having all students graduate from high school prepared for college or careers. The transition to college and career can have more challenges for students with disabilities. On average, students with disabilities who receive special education services earn fewer overall credits, have lower grade point averages, and fail more courses than their general education peers. Course failure and credit deficiency are highly predictive of failing to graduate from high school. Outcomes for those who do graduate are also affected. High school students with an IEP are less likely than their non-IEP peers to have experiences in high school (eg, managing their own bank or credit union account, driving, holding a part-time job) that are associated with success after high school. Additionally, their parents have lower expectations of them with regard to financial independence and independent living. Research has shown that students with intellectual disability, autism, deaf-blindness, multiple disabilities, and orthopedic impairments are at the greatest risk for not transitioning successfully beyond high school.

Regardless the cause, academic difficulties and school failure can have lifelong consequences if not properly diagnosed and addressed. Students with academic, behavioral, and social-emotional struggles are more likely than their peers to drop out of school or engage in behaviors that are dangerous to their health as adolescents. The pediatrician can make a significant difference in outcomes for their patients' educational and school success by helping families engage in healthy development practices and advocating for appropriate assessment of and intervention services for children who are struggling academically.

CASE RESOLUTION

The pediatrician should advise the family to request in writing a psychoeducational evaluation for special education eligibility from the school. The pediatrician can also institute an evaluation for ADHD by gathering information from the family.

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CHAPTER 37

Immunizations

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CASE STUDY

A 20-month-old boy who emigrated with his family from Botswana because his mother is attending graduate school at a local university is brought to the office for a checkup. He has his World Health Organization Expanded Programme immunization card from his homeland showing that he received a BCG vaccine at birth; 3 doses of diphtheria, tetanus toxoids, and pertussis vaccine at 2, 4, and 6 months of age; 3 doses of live oral poliovirus vaccine at 2, 3, and 4 months of age; 3 doses of hepatitis B vaccine at birth and at 2 and 9 months of age; and a monovalent measles vaccine at 9 months of age. It is August, and his parents plan to enroll him in child care; they are eager for him to receive any needed vaccines. His parents report that he is a healthy boy with no immune problems. They report that they will be living with his uncle, who has HIV infection. The boy has had a 3-day history of a runny nose, cough, and tactile fever. His physical examination is normal other than mild clear coryza and a rectal temperature of 37.9°C (100.3°F). The physician must determine what vaccinations may be given to the patient.

Questions

1. What are the different kinds of vaccines?
2. What are the mechanisms of action for live and inactivated vaccines?
3. What are the routinely recommended immunizations for healthy pediatric populations?
4. What are the considerations for immunizing select pediatric populations, such as immunocompromised children?
5. What are reliable resources for up-to-date information about immunizations?
6. How can a pediatrician address parental vaccine refusal?

The Centers for Disease Control and Prevention (CDC) considered immunizations among the top 10 greatest health accomplishments of the 20th century, and vaccines continue to play a major role in the improvement of the health of the world's population. In the United States, the incidence of nearly all the pathogens for which there are routine vaccinations has decreased by 95% to 100% since the early 20th century. The only exception to this is pertussis, which has undergone an approximately 80% reduction. In 2017, the immunization rates for children in the United States remained high, with 84% to 94% of children aged 19 to 35 months immunized for the 4:3:1:3:3 series (4 diphtheria, tetanus toxoids, and acellular pertussis [DTaP]; 3 polio; 1 measles, mumps, and rubella [MMR]; 3 *Haemophilus influenzae* type b [Hib]; 3 hepatitis B virus [HBV]). Worldwide, the percentage of children immunized with 3 doses of diphtheria, tetanus toxoids, and pertussis (DTP) and oral polio vaccines (OPV) and a measles-containing vaccine is at a record high of nearly 85%. Since 1990 the mortality rate has declined for children younger than 5 years in every region in the world, which is directly related to increased rates of vaccinations. Generally, immunizations are safe, well tolerated, and cost-effective, with savings of $5 to $16.50 for every $1 spent.

Another less recognized benefit of vaccinations is that the schedule has essentially provided the backbone for routine pediatric care in the United States, with regular visits scheduled around the recommended intervals for immunizations. These visits have afforded health professionals opportunities for serial evaluation of newborns, infants, and young children as well as education and anticipatory guidance for parents. Increasing availability of new vaccines targeted for older children and adolescents should permit opportunities for improved health care delivery to these age groups. Additionally, health professionals who treat adults have a growing appreciation for the critical role of vaccinations in protecting their patients as well as all members of their patients' family.

General Principles

When planning immunizations for a patient, 2 important factors to consider are the health status of the recipient and the type of immunization to be given. The risks and benefits of using the vaccine in the specific host should be weighed carefully. Vaccines are intended for a host with the capacity for mounting an appropriate immune response, who will likely benefit from the protection provided, and, ideally, who is at little to no risk for adverse effects.

Types of Immunization: Passive and Active

The 2 major types of immunizations are passive and active.

Passive immunization refers to the delivery of preformed antibodies, usually as immune globulin (IG), which may be a general formulation or hyperimmune IG developed with high concentrations of antibodies against a specific disease, such as hepatitis B IG for hepatitis B.

Delivery of IG may be useful in any of the following 3 settings: in a host who cannot manufacture antibodies (eg, congenital immunodeficiency); as a preventive measure, either pre- or post-exposure, especially when the host may be unable to mount an antibody response (eg, immunocompromised naïve child with acute exposure to varicella); or for treatment, in which IG may be used to ameliorate symptoms in the patient in whom disease is already present (eg, intravenous IG for the management of Kawasaki disease).

With *active immunization* all, part, or a modified product (eg, toxoid, purified antigen) of a microorganism is given to the host to elicit an immune response. The intact organisms may be inactivated (ie, killed) or live-attenuated (ie, weakened). Usually, the elicited immune response mimics the response to natural infection and, ideally, poses little to no risk to the recipient.

Inactivated Vaccines

Inactivated vaccines may contain inactivated or killed organisms, purified components (ie, subunit), or inactivated toxins (ie, toxoids) of the organism. These vaccines are not capable of replication in the host. Most inactivated vaccines are delivered by intramuscular injection. Generally, inactivated vaccines may be administered simultaneously with other inactivated vaccines, as well as live viral vaccines.

The common viral vaccines that are inactivated include inactivated influenza vaccine (IIV), trivalent and quadrivalent formulations, hepatitis A vaccine (HAV), HBV, inactivated poliovirus vaccine (IPV), human papillomavirus (HPV), Japanese encephalitis, and rabies vaccines. Toxoid vaccines that are used routinely include tetanus and diphtheria toxoids alone or in combination with whole-cell or acellular pertussis components (eg, DTaP; DTP; tetanus and diphtheria toxoids; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis [Tdap]). The acellular pertussis vaccines are composed of 1 or more purified antigens of *Bordetella pertussis*, in contrast with the whole-cell pertussis vaccines, which are made with killed, whole *B pertussis* organisms. Diphtheria and tetanus toxoids combined with whole-cell pertussis (ie, DTP) vaccines are no longer marketed in the United States but are used in many developing countries. Other inactivated bacterial vaccines include capsular polysaccharide (CPS) vaccines, such as the 23-valent pneumococcal polysaccharide vaccine and tetravalent meningococcal CPS vaccine.

Conjugate Vaccines

Capsular polysaccharide antigens are chemically linked to a protein carrier, which converts the T-cell independent polysaccharides to T-cell dependent antigens. These conjugate vaccines can elicit an immune response, even in young infants. The first CPS-protein conjugate vaccine available was for Hib. The Hib bacterium is covered with a CPS, polyribitol-phosphate. Children younger than 2 years of age are not efficient at mounting antibodies to the polyribitol-phosphate CPS; however, with linkage to a protein carrier the CPS is immunogenic. Since licensure for infants of the Hib conjugate vaccines in 1991, a more than 98% reduction in Hib disease has occurred. With the success of the Hib CPS-protein conjugate vaccines, conjugation techniques have been used for other CPS pathogens, including *Streptococcus pneumoniae* and *Neisseria meningitidis*.

Live-Attenuated Vaccines

Live-attenuated vaccines are infectious agents that replicate in the host to elicit an immune response. The administration is generally not intramuscular but by other delivery routes, such as oral, intranasal, or subcutaneous. Often the live vaccines are viral, including MMR, varicella-zoster virus (VZV), rotavirus, live-attenuated influenza virus (LAIV), OPV, and yellow fever vaccines. Two live bacterial vaccines are available: BCG used against *Mycobacterium tuberculosis* and oral typhoid (Ty21a) vaccine.

A transient suppression of T-cell immunity occurs 2 to 4 weeks after measles vaccination. Because of this, when vaccinating with live viral vaccines, 2 or more live vaccines should be administered at the same time or vaccine administrations should occur at least 4 weeks apart. This principle also holds true for tuberculosis skin testing; either the purified protein derivative should be placed at the same time as a live viral vaccine, or they should be administered at least 4 weeks apart to avoid a false-negative purified protein derivative result because of the transient T-cell suppression. Although this phenomenon has primarily been studied with measles vaccine, the same guidelines should be followed with other live viral vaccines.

Vaccination Schedule

Factors for developing the schedule include the host ability to respond (eg, lost maternal antibody), the need for multiple doses (eg, IPV), the minimal intervals needed between serial doses, and the available products (eg, combination vaccines). Each year, a synchronized immunization schedule is posted by the American Academy of Pediatrics (AAP), American College of Obstetricians and Gynecologists, American Academy of Family Physicians, and the CDC Advisory Committee on Immunization Practices. Separate immunization schedules are available for children from birth through 18 years as well as for adults 19 years and older. The schedules for the United States are posted each January at https://www.cdc.gov/vaccines/schedules. Schedules for countries worldwide are available from the World Health Organization.

Vaccine Recipients

Healthy Pediatric Populations

Routine immunizations on the synchronized schedule are targeted for healthy newborns, infants, children, and adolescents. All licensed vaccines have undergone review by the US Food and Drug Administration (FDA) and have proven safety and immunogenicity or efficacy for the target population. No vaccine is completely free of adverse events or provides 100% protection for every recipient, however. Every effort should be made to provide immunizations when the recipient is healthy and has the best chance to mount an optimal immune response without delaying vaccination or risking a missed opportunity.

Special-Risk Pediatric Populations

Although immune responses to vaccinations are likely most favorable in healthy recipients, a growing segment of the pediatric population has underlying health problems. Because of congenital or acquired immune dysfunctions, some individuals should not receive immunizations as directed by the routine schedules. Special accommodations need to be made for immunizing these individuals, such as adjusting the schedule or possibly not administering some agents. Administration of decreased or partial doses of vaccines is not indicated. Some of the select populations or circumstances that warrant special consideration include immunocompromised status, immunodeficiency, pregnancy, preterm birth status, low birth weight status, allergy to egg protein, planned international travel, patients from other countries, adolescence, and vaccines administered in other countries.

Immunocompromised Child

The vaccination plan for the immunocompromised child should be determined by the nature and degree of immunosuppression. The health professional should weigh risks and benefits for each child individually, with consideration for some general principles. For example, live vaccines should not be given to severely compromised individuals because of the possible risks. In general, inactivated vaccines may be safely administered to nearly all recipients; however, immunocompromised individuals may not mount an optimal immune response. In this setting, the health professional should attempt to adjust timing of vaccination to optimize the chance of a good immune response. Guidelines for immunizing immunocompromised children and adults have been established by the Infectious Diseases Society of America in conjunction with the AAP, CDC, and other professional groups and are posted at www.idsociety.org/Templates/Content.aspx?id=32212256011.

Types of Immunodeficiency

Newborns, infants, and children may have abnormalities of any aspect of the immune system, which may affect their ability to receive vaccinations. Weighing the risks of both the disease and the vaccine and the benefits of protection is essential. A reasonable approach to developing a vaccination plan for children with immune abnormalities is to consider the mechanism of immune defense against the vaccine agents; if the needed defense mechanism is deficient, immunizing with that agent may not be appropriate. For example, cellular immunity is essential in defending against viral agents. Thus, children with abnormalities of cell-mediated immunity, whether primary or acquired, may not be candidates for live viral vaccines.

Primary immunodeficiencies are generally inherited, and secondary immunodeficiencies are acquired. Examples of acquired immunodeficiencies include HIV infection, malignancy, and illnesses (eg, malnutrition, uremia) as well as those caused by medications (eg, chemotherapy, immunosuppressive agents). The OPV is contraindicated for individuals with primary humoral immunity abnormalities (ie, those who cannot make antibodies); however, MMR vaccine may be indicated for some of these individuals because of the potential risks of natural infection. Receipt of all vaccines, including live viral vaccines, is acceptable for most individuals with complement deficiencies. For abnormal phagocytic function, live bacterial vaccines should not be given. For individuals with traumatic or surgical asplenia, vaccination with pneumococcal, meningococcal, and Hib vaccines is indicated and should be considered emergently in the case of trauma. Chemoprophylaxis also may have a role in protection for compromised individuals.

For children with immunocompromised household contacts, it is generally acceptable for them to receive MMR, VZV, and oral rotavirus vaccines. However, the live viral vaccines of OPV and LAIV should not be given in some settings. In contrast, use of some vaccines, such as IIV, is encouraged to protect the vaccinated individuals as well as their compromised contacts.

Pregnancy

Pregnancy is associated with some impairment of cell-mediated immunity. With this decreased immunity, pregnant women may not mount protective immune responses to some infectious agents. Thus, in general, live vaccines should not be administered to pregnant women; however, the risks and benefits should be weighed for each individual patient. Live-attenuated influenza virus should not be given to pregnant women. Neither should rubella vaccine be given to pregnant women, although no cases of rubella embryopathy following inadvertent immunization of a pregnant woman have been reported.

Both IIV and Tdap are recommended during pregnancy to provide protection for the mother and the fetus. These vaccines may be given anytime during pregnancy, although the preferred timing for Tdap administration is 27 through 36 weeks to optimize transfer of pertussis antibodies to the fetus. Pediatricians are often asked whether administration of live viral vaccines is contraindicated for children residing with a pregnant household contact; generally, such administration is not contraindicated.

Preterm and Low Birth Weight Infants

In general, medically stable preterm (<37 weeks of gestation) and low birth weight infants (<2,500 g [<5 lb 5 oz]) may be immunized at the same dose, schedule, and postnatal age as full-term and normal birth weight infants.

Special consideration should be given to use of HBV vaccine in newborns weighing less than 2,000 g (<4 lb 4 oz) as follows. For the hepatitis B surface antigen (HBsAg)-positive mother or mother whose status cannot be determined within 12 hours, monovalent hepatitis B vaccine and hepatitis B IG should be administered within 12 hours of birth. The birth dose of vaccine does not count as part of the series; thus, the infant requires 3 additional vaccine doses starting at 1 month of age. The HBsAg and antibodies should be checked after completing the vaccine series, usually at the 9- or 12-month check-up. For the HBsAg-negative mother, monovalent hepatitis B vaccine is administered to the newborn at 1 month of age (sooner if the newborn is stable for discharge), after which the usual schedule

is followed, such that the infant receives a total of 3 doses. Serologic testing is not necessary.

Other Conditions Affecting Immunization Schedule

Allergy to Egg

Children with allergic reactions to egg protein—including severe hypersensitivity—are at low risk for anaphylactic reactions to measles, mumps, and influenza (both IIV and LAIV) vaccines. Special precautions for immunizing children with egg allergy are no longer routinely recommended.

Yellow fever vaccine may contain egg protein in higher concentrations than in influenza vaccines and may rarely induce an immediate allergic reaction. Guidelines for skin testing and graded vaccine dosing are provided in the vaccine package insert.

International Adoptees, Travelers, Immigrants, and Refugees

Travel is not restricted to persons of any particular socioeconomic status; thus, physicians should inquire about foreign travel in all routine clinical visits. In preparing patients for travel, the health professional should review the child's record to ensure that all routine vaccines are up-to-date. The child should receive vaccinations and other preventive measures (eg, malaria prophylaxis) targeted for his or her destination. An accelerated schedule may be necessary, for example, early administration of MMR for infants 6 to 12 months of age traveling to a measles-endemic area. Use of IG prophylaxis to prevent HAV is recommended for susceptible individuals who are not candidates for active immunization (eg, too young to receive the HAV vaccine, immunocompromised status) traveling to areas with elevated risk of hepatitis A. To help ensure healthy travel, the health professional should check the current recommendations for the traveler's destination at the CDC Travelers' Health website (https://wwwnc.cdc.gov/travel) and the World Health Organization International Travel and Health website (www.who.int/ith/en).

Immigrants, refugees, and international adoptees often have health care issues. Immunization status, underlying health, and possible intercurrent illnesses should be evaluated soon after arrival. Many of these children have been in poor living conditions and exposed to health hazards of environments such as refugee camps and orphanages. The United States requires proof of the first dose of vaccines for entry into the country, although exemptions exist for refugees and adoptees younger than 10 years of age. Often these high-risk children have not been immunized or their records are missing. Written, dated, and appropriate records (ie, patient age, dates, interval, number of doses) may be considered valid, and subsequent immunization may resume according to the US schedule. Another option, especially in cases in which documentation is questionable, is to perform serologic studies for antibodies to vaccine antigens with available valid testing.

Adolescents

The AAP recommends a routine health visit at 11 to 12 years of age, including receipt of immunizations needed for adolescents. One of these vaccines is Tdap for use as a single booster dose at 11 to 18 years of age. Currently, Tdap is licensed only for a single booster dose. Off-label use of additional doses is recommended in special situations, however, such as during pregnancy and for close contacts of infants. With recognition of waning vaccine-induced immunity to pertussis, additional Tdap doses may be routinely recommended in the future.

Meningococcal vaccine and HPV are also indicated for adolescents at the 11- to 12-year-old visit. Four meningococcal vaccines are available in the United States: 2 CPS-protein conjugate vaccine (meningococcal conjugate vaccine [MenACWY]), and 2 B meningococcal (MenB) vaccines. The CPS vaccines contain 4 serotypes (A, C, Y, and W-135). The MenACWY-D vaccine (Menactra) is licensed for use in persons age 9 months to 55 years. The MenACWY-CRM vaccine (Menveo) is licensed for use in persons age 2 months to 55 years. Routine immunization with MenACWY is recommended at age 11 to 12 years, with a booster dose at age 16 years. For adolescents who received the first dose between age 13 and 15 years, the second dose may be given at ages 16 to 18 years (up to 5 years after the first dose); however, no booster dose is needed for teenagers who receive their first dose at age 16 years or older. The MenACWY vaccine is also recommended for catch-up dosing for older adolescents who have not been immunized, as well as for individuals 9 months to 55 years of age who are at increased risk of meningococcal diseases. The 2 MenB vaccines (Bexsero and Trumenba) are prepared using different virulence factors of the bacteria. The vaccines are licensed for individuals 10 through 25 years of age and recommended for those at increased risk of meningococcal infection. The vaccines may also be used during MenB outbreaks. The MenB vaccines are not routinely recommended at the 11- to 12-year-old visit.

The only HPV vaccine available in the United States is 9-valent (9vHPV) and is recommended for routine use in adolescents at 11 to 12 years of age. The vaccine is composed of virus-like particles prepared from recombinant L1 capsid protein. The 9vHPV vaccine (Gardasil 9), contains serotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58 and it is licensed for females and males age 9 through 26 years to protect against cancers caused by HPV infections. For individuals younger than 15 years, 9vHPV is administered in a 2-dose regimen, with the second dose given 6 to 12 months after the first dose. For those age 15 years and older, 9vHPV is given in a 3-dose regimen at day 0, 1 to 2 months, and 6 months.

In addition, at adolescent visits (including precollege visits), health professionals should review the patient's records to ensure that all recommended vaccines have been received, inquire about household contacts of infants or compromised hosts, and provide anticipatory guidance for safe and healthy living for the adolescent and parent.

Immunizations Received in Other Countries

Most vaccines used worldwide are produced with adequate quality control and may be considered reliable. Healthy immigrants immunized in countries outside the United States should receive vaccines according to the recommended schedule for age in the

United States. Only written documentation should be accepted as proof of previous vaccination. Written, dated, and appropriate records (ie, correct age, dates, interval, number of doses) may be considered as valid, and immunizations may resume according to the US schedule.

Although most globally prepared vaccines are acceptable, concern may exist for vaccine potency because of unsuitable storage and handling. Other concerns include inaccurate documentation and inadequate immune response in some children resulting from other factors (eg, malnutrition, underlying illness). If vaccination status is uncertain, options include vaccinating with the antigen in question or, if available, serologic testing. Generally, receipt of additional doses of diphtheria and tetanus toxoids alone or in combination with a pertussis-containing vaccine (ie, DTP, DTaP, tetanus and diphtheria toxoids, Tdap) may result in an increase in reactions (especially injection site reactions), and checking antibody titers against diphtheria and tetanus toxoids is encouraged. Currently, commercially available assays for pertussis antibodies are of unknown clinically accuracy and testing is not recommended. A serological assay developed by the CDC and FDA has been used to confirm the diagnosis of pertussis, especially during outbreaks. For other vaccines, if the status is unknown, vaccination may be performed because extra doses are generally well tolerated. Additionally, extra doses are less expensive and more time efficient than performing serology. Most developing countries do not have VZV, conjugated pneumococcal, or Hib vaccines; thus, these should be given as indicated per the US schedule.

Adverse Events and Vaccine Information

Adverse Events

As noted previously, no vaccine is completely free of adverse events, and known adverse events should be discussed with non-minor vaccine recipients or the parent(s)/legal guardian(s) of the minor vaccine recipient. In addition to discussing the risks and benefits of vaccination, health professionals should include education about the risks associated with the natural disease. This is especially important today, because many individuals have not seen the diseases that vaccines have been successful in controlling or eradicating.

In addition to safety information from the AAP and CDC, the manufacturer's package insert provides information about the rates of adverse events and contraindications for the specific vaccine. Most adverse events observed following routine immunizations are local injection site reactions (eg, erythema, swelling, pain) and systemic reactions (eg, fever, fussiness). Although most of these adverse events are mild and self-limiting, some may be associated with significant dysfunction for the child (eg, not using a limb because of pain).

Rarely, serious adverse events may occur following immunization, and these may be associated with permanent disability or life-threatening illness. The occurrence of an adverse event after immunization does not prove a cause-and-effect relationship of the vaccine and the event but a temporal relationship. If a vaccine recipient experiences a serious adverse event, a complete evaluation for all plausible causes, including the role of the vaccine antigen, should be performed. Additionally, all clinically significant adverse events should be reported to the Vaccine Adverse Event Reporting System (https://vaers.hhs.gov), which is maintained by the CDC and FDA. Adverse event reporting is important because it helps identify possible unexpected events that were not observed in pre-licensure clinical trials.

Precautions and Contraindications

The Vaccine Information Statement (VIS) and package insert provide information for health professionals, the non-minor vaccinated individual, and the parent(s)/legal guardian(s) of minor vaccinated individuals about the precautions and contraindications for specific products.

A *precaution* suggests that careful analysis of risks and benefits of the vaccine should be performed; if benefits outweigh risks, the vaccine may be given. A *contraindication* means that a vaccine should not be administered. An example of a contraindication is known anaphylaxis to any component of the vaccine. Breastfeeding does not interfere with oral immunization with rotavirus or OPV vaccines and is not a contraindication.

Minor illness without fever (temperature ≤38°C [≤100.4°F]) should not be considered a contraindication to vaccination. Temperature above 38°C (>100.4°F) may not be a contraindication, depending on the physician's assessment of the child, the illness, and the particular vaccine. If the child is evaluated early in the disease process and the course is not predictable or the illness is moderate to severe, delaying immunization is reasonable. Deferring immunization without appropriate justification can cause a missed opportunity and may result in inadequate immunization of the child.

Informing Vaccine Recipients and Parents and Vaccine Refusal

Vaccine recipients and parents should be informed about the risks and benefits of vaccination and the disease the vaccine is designed to prevent. The National Childhood Vaccine Injury Act of 1986 requires that parents receive a VIS each time a child receives a vaccine covered under this legislation, whether the vaccine was purchased with public or private funds. The VISs are available from the CDC (www.cdc.gov/vaccines/hcp/vis/index.html). Health professionals should document in the patient's chart the vaccine manufacturer, lot number, and date of administration and that VISs were provided and discussed with the non-minor vaccinated individual and the parent or legal guardian of the minor vaccinated individual.

In the United States, proof of immunization is required for entry into elementary and secondary school. In addition, some child care centers and colleges also require vaccines for entry. All states permit medical exemptions (eg, immunocompromised child), and most states have provision for religious or philosophic exemption for individuals whose beliefs prohibit immunizations. Three states—California, Mississippi, and West Virginia—do not permit personal belief exemptions for children attending child care or schools. Less than 1% of US children are from families who refuse all vaccines. An increasing number of parents decline some

immunizations for their child, however, despite best efforts to educate parents about the effectiveness of vaccines and the realistic chances of vaccine-associated adverse events. At times, parents have a genuine fear of the risks of vaccines without fear of the natural disease, because many parents have not seen the diseases in the current, post-vaccine era. For others, their exaggerated fear of vaccine risks results from deeply held family beliefs, or their fears are fueled by biased anti-vaccine information presented in the media without scientific support.

A reasonable approach for the health professional is to address the concerns of parents or guardians in a non-condescending fashion, provide education about the known risks and benefits of immunization, and initiate a candid discussion of the risks of the natural infections. The discussion should be documented in the child's chart and the topic revisited at future encounters. The AAP encourages a presumptive rather than a participatory approach in counseling about vaccinations. With the *presumptive approach*, instead of asking the parents or guardians whether they want the vaccines to be administered, the pediatrician informs them that shots are due. Researchers have shown that parents with whom this strategy is used are more likely to accept vaccines. Because of strong convictions that immunization benefits outweigh risks, some health professionals choose not to provide care for children of families who refuse vaccines.

Vaccine Information

Information about current immunizations for health professionals and laypersons is available from many resources, including the CDC, AAP, FDA, and World Health Organization (Table 37.1). Multiple web-based applications with vaccine information are available for smart devices from the AAP and US Department of Health and Human Services (ie, CDC, FDA, National Institutes of Health), as well as other professional organizations.

Table 37.1. Internet Sources of Vaccine Information

Source	*Website*
American Academy of Pediatrics	www.aap.org
Centers for Disease Control and Prevention	www.cdc.gov/vaccines/schedules
Vaccine-Specific Advisory Committee for Immunization Practices Recommendations	www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html
Morbidity and Mortality Weekly Report	www.ncbi.nlm.nih.gov/pubmed/11848294
US Food and Drug Administration: Vaccines Licensed for Use in the United States	www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833
Vaccine Adverse Event Reporting System	https://vaers.hhs.gov/
World Health Organization	www.who.int/en
Gavi, the Vaccine Alliance	www.gavialliance.org

CASE RESOLUTION

The boy was appropriately immunized for Botswana recommendations through the age of 9 months; however, his immunizations are considered delayed according to the US schedule. He is past due for the fourth dose of DTaP and the first dose of MMR and VZV vaccines. Additionally, he has not received HAV or any conjugate vaccines. The dose of monovalent measles vaccine does not change his need to receive 2 doses of MMR and VZV vaccines after age 12 months in the United States. His uncle's immune status does not affect his receipt of MMR or VZV vaccines. His current respiratory illness is considered mild, and he does not have significant fever (<38°C [<100.4°F]); thus, his illness does not preclude him from receiving immunizations.

During this visit, he may receive DTaP, the first dose of MMR plus VZV (alone or as a combination MMRV); 1 dose of Hib conjugate vaccine; dose 1 of 2 of conjugate pneumococcal vaccine, which should be administered 2 months apart; and dose 1 of 2 of HAV, which should be administered at least 6 months apart. He is too old to receive the oral rotavirus vaccine. All VISs should be provided. The patient is scheduled to return in 2 months (ie, in October) for his next dose of conjugate pneumococcal vaccine and dose 1 of 2 of IIV. He will need a fourth dose of inactivated poliovirus vaccine before school age.

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CHAPTER 38

Health Maintenance in Older Children and Adolescents

Monica Sifuentes, MD

CASE STUDY

Before a 13-year-old girl enters a new school, she is required to undergo a physical examination. She has not seen a primary care physician in many years and has been healthy. Currently she has no medical complaints. Her examination is completely normal.

Questions

1. What are the important components of the history and physical examination in healthy older children and adolescents?
2. What immunizations are recommended for older children and adolescents?
3. What laboratory tests should be performed at health maintenance visits? Why?
4. What are significant topics to cover for anticipatory guidance in this age group?

Older children and adolescents are generally healthy individuals who infrequently visit physicians. If they are seen by a doctor, the visits are often for acute complaints, such as upper respiratory infections or sports-related injuries, and are, therefore, generally problem oriented. Statistics on health maintenance visits in this age group are not readily available because patients may go to several different sites for health care and often do not receive consistent comprehensive care at any of these places for a variety of reasons. Older children and adolescents seek treatment for acute and chronic conditions in private offices, urgent care centers, public health clinics, community and school health clinics, hospitals, and emergency departments. It has been reported that fewer than 50% of adolescents consistently receive a preventive health care visit during any given year, and the same percentage probably applies to older children as well.

This all-too-common practice of inconsistent health care contributes to missed opportunities for anticipatory guidance, health education, and screening for preventable conditions. Screening tests also can be used to identify treatable conditions such as hypertension, anemia, and tuberculosis. Ideally, older children and adolescents should receive recommended immunizations beginning at 11 to 12 years of age; screening for depression; counseling concerning sexual activity, contraception, and sexually transmitted infections (STIs), including HIV; reassurance to address their emotional well-being; guidelines for adequate nutrition, sleep hygiene, and screen time; education about tobacco, e-cigarettes and vaping, illicit drugs, and alcohol; and information about physical fitness and exercise as well as violence and injury prevention.

Guidelines for preventive child and adolescent health care have been published by the American Academy of Pediatrics (AAP) in conjunction with the Maternal and Child Health Bureau, US Child Health and Disability Prevention Program, AAP Section on Adolescent Health, and American Medical Association. Box 38.1 is a brief summary of these guidelines for older children and adolescents.

Health Maintenance Visit

The purpose of the health maintenance visit for an older child or adolescent is to assess their general physical health, mental and psychological health, and overall well-being and establish an independent relationship between the patient and health professional for open communication and trust for future visits. Initial questions asked during this visit should be simple and focused on how the patient feels in general about his or her health, physical growth and development, and existing relationships with family and friends. More specific questions can then be formulated depending on the patient's responses. In healthy patients, the medical history can be obtained using a questionnaire that parents and children complete in the waiting room. If this method is used, a separate form should be given to the adolescent if they are accompanied by a parent or guardian. The information is then reviewed at the start of the interview. Chronic medical conditions should be addressed at this time.

Medical History

Older children and adolescents should always be questioned directly about their medical history (Box 38.2). The parent or guardian should be encouraged to participate only after the child or adolescent

Box 38.1. Guidelines for Adolescent Health Maintenance Evaluation

Screening History

- Eating disorders
- Gender identification
- Sexual orientation
- Sexual activity (consensual and nonconsensual)
- Tobacco, e-cigarettes, or vaping use
- Alcohol use/abuse
- Drug use/abuse (CRAFFT questionnaire[a])
- School performance
- Depression
- Risk for suicide

Physical Examination

- BMI
- Blood pressure
- Comprehensive examination
- Genital examination
- Pelvic examination[b]

Universal and Selective Screening Laboratory Tests/Studies

- Snellen test
- Audiometry
- Hemoglobin or hematocrit
- Tuberculin skin test or blood test (IGRA)
- Cholesterol (If the patient is obese or there is a significant family history of hyperlipidemia, consider other laboratory tests, such as fasting glucose and lipid panel.)
- If sexually active
  - Urine hCG
  - Urine or vaginal NAAT for gonorrhea/chlamydia
  - Serum HIV, RPR, hepatitis C[c]
  - Papanicolaou test[b]

Anticipatory Guidance and Counseling

- Parenting/communication
- Pubertal development
- Diet/nutrition, including calcium and vitamin D supplementation
- Exercise
- Injury prevention
- Screen time/social media
- Educational or vocational plans/goals
- Lifestyle modifications
  - Gender and sexual identity
  - Abstinence
  - Safe sexual activity
  - Other reproductive health issues
  - Contraception
  - Avoidance of tobacco, e-cigarettes, vaping, alcohol, and prescription and illicit drugs
  - Identifying feelings of sadness/anger

Abbreviations: BMI, body mass index; CRAFFT, car, relax, alone, forget, friends/family, trouble; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IGRA, interferon gamma release assay; NAAT, nucleic acid amplification test; RPR, rapid plasma reagin.

[a] See Chapter 63 for information about the CRAFFT questionnaire.

[b] A pelvic examination with a Papanicolaou test is recommended within 3 years of the onset of sexual activity (American Cancer Society) or age 21 years (American Congress of Obstetricians and Gynecologists). For indications for a pelvic examination, see Chapter 58.

[c] If patient engaged in injection drug use or young man having sex with men.

Box 38.2. What to Ask

Screening in Older Children and Adolescents

Questions for Patient and Parent

- How has the child or adolescent been doing lately? Does the parent have any complaints or concerns?
- How does the child or adolescent like school? How is he or she doing academically and socially? What are his or her future goals?
- What activities does the child or adolescent currently participate in, including work?
- Does he or she have any hobbies?
- With whom does the child or adolescent live?
- Are there any significant illnesses in the immediate or extended family, such as hypertension, diabetes, or cancer?
- Does the child or adolescent take any medications, herbs, or supplements (prescribed or over-the-counter) regularly?

Questions for Child or Adolescent Alone

- Do you have any questions or concerns?
- How are things at home? Are there any problems with parents or siblings? Do you feel safe at home and school?
- Are you attending school?
- Do you like school? Who do you hang out with at school?
- Have you ever been truant, suspended, or expelled?
- What do you like to do for fun?

(See Chapter 4 for the rest of the interview.)

has responded to questions or if invited by the child or adolescent to assist with the interview. The degree of parental participation also is influenced by the current cognitive and developmental stage of the patient.

Psychosocial History

The psychosocial component of the interview should be conducted with older children or adolescents alone as well as together with parents or guardians after the issue of confidentiality has been reviewed (see Box 38.2). General questions about school, outside activities or hobbies, and family are often less threatening than inquiries about friends and high-risk behavior such as tobacco use. More sensitive topics relating to drug use, sexuality, gender identification, sexual orientation, and sexual activity should be addressed confidentially after parents or guardians have left the room. Subjects initially discussed with parents should be reviewed once again with teenagers alone.

A useful tool for conducting the psychosocial interview has been developed and refined by physicians who specialize in pediatrics and adolescent medicine. Known by the acronym HEADSS, it reviews the essential components of the psychosocial history: *h*ome, *e*mployment and *e*ducation, *a*ctivities, *d*rugs, sexuality, and *s*uicide/depression (see Chapter 4). Additional inquiries should be made about social media usage, including its influence on sleep hygiene. Some authors have suggested that this should be the third S in the HEADSS acronym.

Dietary History

A general dietary history should be obtained, with particular focus on eating habits, level of physical activity, and body image. Dietary restrictions, if any, should be investigated to assess for possible deficiencies in minerals and vitamins as well as the presence of disordered eating. Daily calcium, vitamin D, and iron intake should be reviewed, especially in adolescent females. Adolescent males should be asked about nutritional supplements.

Family History

Significant illnesses, such as hypertension, hyperlipidemia, obesity, and diabetes, in first- and second-degree family members should be reviewed. Family use of alcohol, tobacco, and illegal as well as prescribed substances also should be determined. Age and cause of death in immediate family members should be recorded.

Medications and Allergies

Prescription as well as nonprescription (over-the-counter) medications, herbs, and supplements should be reviewed along with the indications and frequency of usage.

Physical Examination

The height and weight of patients should be plotted on a growth curve, with particular attention paid to the velocity of growth and body mass index (weight [kg]/(height [m])^2). Blood pressure also should be noted and compared with age- and height-related reference values.

Aspects of the physical examination that are influenced by puberty should be emphasized. The skin should be carefully inspected for acne and hirsutism; clinicians should offer treatment whether or not patients acknowledge that they have skin problems. Tattoos, piercings, and signs of abuse or self-inflicted injury (ie, cutting) also should be noted. The oropharynx should be examined for any evidence of gingivitis or other signs of poor dental hygiene or malocclusion. The neck should be palpated for adenopathy and the thyroid gland for hypertrophy or nodules, especially in adolescent females. The back should be examined for any evidence of scoliosis, which is important to diagnose during this time of rapid growth.

Assessment of the pubertal development of the breasts and genitalia in preadolescent or adolescent females and the genitalia, including presence of pubic hair, in adolescent males is essential. The sexual maturity rating (SMR) (ie, Tanner stage) can then be correlated with other signs of puberty, such as the appearance of acne and body odor. For example, the adolescent female with SMR 4 breasts and immature pubic hair distribution may have an underlying problem, such as complete androgen insensitivity syndrome (also called testicular feminization syndrome).

The abdomen should be palpated for organomegaly and the testicles for masses, hydroceles, hernias, or varicoceles. Lesions such as warts or vesicles also should be documented. The external female genitalia should be inspected for similar lesions and to document Tanner stage development. A speculum examination should be performed in females who are sexually active and report vaginal discharge, unexplained vaginal bleeding, or lower abdominal pain. (See Chapter 58 for additional indications for a pelvic examination.) A speculum examination is otherwise not indicated in an asymptomatic sexually active female. In general, virginal girls with normal pubertal development do not require a speculum examination; gentle inspection of the external genitalia is adequate in most cases, with special attention to the SMR and hymenal patency. A rectal examination is generally reserved for patients with chronic abdominal pain or other specific acute gastrointestinal symptoms.

Immunizations

Many recent modifications have been made to the preadolescent/adolescent vaccination schedule (Table 38.1). As always, health professionals should verify that patients have completed the primary immunization series. If not, they should be given catch-up doses according to the most recent Advisory Committee on Immunization Practices and Centers for Disease Control and Prevention recommendations. The tetanus and diphtheria toxoids and acellular pertussis (Tdap) (eg, Adacel, Boostrix), human papillomavirus (HPV) (eg, Gardasil 9), and meningococcal conjugate (MCV4) (eg, Menactra, Menveo) vaccines should be given to preteens at the 11- to-12-year visit. The Tdap vaccine has replaced the tetanus/diphtheria booster previously given at this age. Pertussis was added to the booster because immunity to pertussis has been noted to wane 5 to 8 years after vaccination, and there has been an increasing prevalence of pertussis detected in adolescents and adults with chronic cough in many communities. A conjugate vaccine against *Neisseria meningitidis* (MCV4) was approved by the US Food and Drug Administration in 2005. The Advisory Committee on Immunization Practices recommends that MCV4 be given to all 11- to 18-year-olds. Although there are 3 different vaccines (ie, Gardasil, Cervarix, and Gardasil 9) available that include protection against 2 of the HPV types that

Table 38.1. Recommended Immunization Schedule Affecting Adolescents

	Recommended Age (years)	
Vaccine Type	*11–12*	*13–18*
Tetanus, diphtheria, pertussis	Tdap	Tdap (catch-up)
HPV	HPV (2 doses)	HPV (catch-up) (2 or 3 doses)[a]
Meningococcal Meningococcal serogroup B	MCV4	MCV4 (booster at 16 years) Individual clinical decision at age 16–23 years if not at increased risk
Varicella	Varicella 2-dose series	
Influenza	Influenza annually	

Abbreviations: HPV, human papillomavirus; MCV4, meningococcal conjugate vaccine; Tdap, tetanus and diphtheria toxoids and acellular pertussis.

[a] 2- or 3-dose series depending on age at initial vaccination (see Chapter 37).

Modified from Centers for Disease Control and Prevention. Child and adolescent immunization schedule (birth through 18 years). https://www.cdc.gov/vaccines/schedules. Reviewed February 5, 2019. Accessed September 2, 2019.

cause most cervical cancers (oncogenic types 16 and 18), only the 9-valent product is currently used in the United States. Licensed in 2015, Gardasil 9 protects against 5 additional HPV types that cause an additional 10% of HPV-associated cancers in the United States. While there has been much publicity and some controversy surrounding the HPV vaccine, current recommendations state that all adolescents should begin the HPV vaccination series routinely at 11 to 12 years of age with the goal of completing the series by age 13 years. The vaccine is approved for patients as young as 9 years. For those who initiate the series at 9 to 14 years of age, a 2-dose series is administered rather than the 3-dose series for those who begin vaccination at age 15. Gardasil 9 also should be routinely administered to young adults through the age of 26 years who have not received the vaccine. Ideally, the vaccine should be administered before the initiation of sexual activity because Gardasil 9 is only preventive and does not treat or cure HPV infection, dysplasia, or cancer that has already developed in response to HPV exposure. However, regardless of previous sexual exposure, the HPV vaccine should be administered to all adolescents, even if they are already sexually active.

Recommendations concerning some of the older, traditional vaccines have changed, as have the catch-up schedules. The adolescent (13 years and older) with no evidence of immunity to varicella should receive 2 doses of the vaccine at least 4 weeks apart. If an adolescent or preadolescent has received only 1 dose of the varicella vaccine, a second dose should be administered. Routine vaccination against hepatitis B also is recommended, regardless of sexual activity, if it has not been administered previously. The 2-dose hepatitis A series should be given to all teenagers not previously vaccinated if they reside in high-incidence communities. Influenza vaccine should be given annually to all infants 6 months and older, children, and adolescents and to those who come into close contact with individuals with high-risk conditions. Two meningococcal serogroup B vaccines (ie, Bexsero, Trumenba) are currently licensed for use among persons aged 10 to 25 years in the United States and are used routinely for individuals 10 years and older who are at high risk for serogroup B meningococcal disease, such as those with anatomical or functional asplenia or persistent complement deficiencies. Adolescents and young adults aged 16 to 23 years also may be vaccinated to provide short-term protection during serogroup B meningococcal disease outbreaks. Pneumococcal vaccine should be offered to high-risk groups, such as those with chronic lung disease, cyanotic congenital heart disease, and diabetes mellitus. In addition, a Mantoux skin test for tuberculosis should be performed if the adolescent resides in a high-risk environment. A tuberculosis blood test (also called an interferon gamma release assay) is preferred if the patient has received the tuberculosis or BCG vaccine or has a difficult time returning for a second appointment to look for a reaction to the Mantoux skin test. (For complete recommendations, see Chapter 37.)

Laboratory Tests

A hemoglobin level should be obtained to evaluate for anemia. Although previously included in laboratory screening, a urinalysis is no longer recommended to assess for protein, blood, and pyuria because most abnormal findings resolve spontaneously. Other suggested screening tests include hearing and vision tests and a cholesterol and lipid profile, once between 9 and 11 years and a second time between 17 and 21 years of age.

In addition to these laboratory tests, sexually active adolescents should be screened for STIs. If a pelvic examination is performed, an endocervical specimen should be obtained for nucleic acid amplification testing for gonorrhea and chlamydia. However, if a pelvic examination is not indicated, routine screening for gonorrhea and chlamydia may be performed with a urine or vaginal sample alone using nucleic acid amplification testing methods. The 2015 recommendations from the Centers for Disease Control and Prevention state that all sexually active women younger than 25 years should be screened annually. Males should be screened in high-prevalence clinical settings, such as adolescent clinics, correctional facilities, or STI clinics; if they are symptomatic; if they have a history of multiple partners and unprotected intercourse; or if they are having sex with men. In addition, a rapid plasma reagin test for syphilis and an HIV test should be obtained, especially if another STI is suspected or confirmed. All these tests should be offered in the clinically appropriate setting after patients have received adequate education on STIs, with a follow-up visit scheduled to discuss the results.

Patient Education

At the conclusion of the health maintenance visit, positive as well as negative findings should be reviewed with patients and their parents or guardians. Depending on the nature of these findings and the age of the patient, the health professional may initially choose to address these findings with the patient alone, keeping in mind issues of confidentiality. All recommended screening laboratory studies and immunizations should be reviewed before their administration, including the need for further follow-up. Subsequent vaccine doses must be outlined for patients and parents or guardians. The timing of the next visit and reasons for this visit should be discussed.

The remainder of the health maintenance visit should be spent addressing any specific concerns of patients and parents or guardians,

highlighting health care problems (eg, obesity, high blood pressure), and identifying any factors that may be contributing to high-risk behavior, such as drug or alcohol use. Older children or adolescents who are not participating in any deleterious activities should be praised for their positive behavior as well as provided with educational information such as materials addressing injury prevention and sleep hygiene.

Preparticipation Physical Evaluation for School-age and Adolescent Athletes

The preparticipation physical evaluation (PPE) is essentially the "sports physical" that many schools require for participation in organized athletic programs. The primary objective of the PPE is to assess the athlete's readiness to compete safely and effectively in training and competition. Ideally, it also should identify athletes at risk of injury, reinjury, or sudden death, as well as those with an underlying medical condition that may preclude safe athletic participation.

Historically, controversy existed about the appropriate location for performance of the PPE. Community physicians were often asked to perform limited en masse examinations at schools, or a group of clinicians was asked to perform the examinations in the gymnasium using "stations." Either way, the patient did not truly receive a complete physical examination or assessment, and neither approach lent itself to privacy. In addition, parents had a false sense of security and believed that their children had received adequate medical care. The AAP, in conjunction with other professional organizations, has developed a monograph that includes guidelines for the PPE. Ideally, primary care physicians should perform the PPE annually in their office during a scheduled visit at least 4 to 6 weeks before the beginning of the athletic season. Pediatricians can also use this required visit as an opportunity to perform an annual comprehensive health maintenance examination on older children and adolescents, including providing important anticipatory guidance, administering catch-up immunizations, and performing the various screening tests recommended for this age group.

History

The most challenging aspect of the PPE is reviewing the past medical and family history with the athlete to uncover previously unrecognized abnormalities of the cardiovascular system that warrant further investigation by a cardiologist prior to participating in a given sport. Red flags include a history of congenital heart disease, cardiac channelopathies (eg, long QT syndrome), a history of Kawasaki disease and associated coronary artery anomalies, and a history of myocarditis. The rest of the medical history for the PPE should focus on previous athletic participation and any current or past injuries that have required immediate evaluation and subsequent bracing, casting, surgery, or missed practice or play (Box 38.3). A standard questionnaire codeveloped by the AAP for this purpose may be used in the office setting. In addition, many health professionals record the results of the physical examination as well as their recommendations for the degree of athletic participation on this standard form (Figures 38.1 through 38.4). A review of systems should specifically include an inquiry about a history of syncope, near-syncope, chest pain, palpitations, and excessive shortness of breath or fatigue with exertion.

Box 38.3. What to Ask

Preparticipation Physical Evaluation

- What sport(s) does the child or adolescent wish to participate in? Has he or she participated in this sport in the past?
- Has the child or adolescent ever experienced a sports injury? If so, how much time did the athlete refrain from sports activities as a result of this injury?
- Has the athlete ever experienced a lapse of consciousness or concussion?
- Does the child or adolescent have a significant underlying health problem?
- Is the child or adolescent taking any prescribed or over-the-counter medications, supplements, or caffeine?
- Does the child or adolescent have any allergies?
- Has the child or adolescent ever had syncope or near-syncope, palpitations, chest pain, discomfort, or shortness of breath during exercise or at rest?
- Does the child or adolescent have a family history of sudden, early, nontraumatic deaths in a first- or second-degree relative younger than 50 years?

Physical Examination

A complete physical examination should be performed. If circumstances preclude this, specific attention should be paid to the eyes, heart, abdomen, skin, and musculoskeletal system. Height, weight, blood pressure, and visual acuity also should be measured. Examination of the eyes is essential to document physiological *anisocoria* (different papillary diameters). A thorough cardiac evaluation for murmurs, abnormal heart sounds, or arrhythmias should be performed with the patient supine and again standing or straining during the Valsalva maneuver. The abdomen should be palpated for an enlarged liver or spleen, especially in the adolescent with a recent viral illness that could suggest mononucleosis. In males, the genitalia should be examined for sexual maturity in addition to assessing for abnormalities, such as atrophy, absence of a testis, or presence of a testicular mass or inguinal hernia. The skin should be inspected for lesions, such as tinea corporis, molluscum contagiosum, scabies, impetigo, or herpes simplex infection.

The 2-minute orthopedic examination consists of a head-to-toe assessment of all muscle groups and joints; any deformities, anomalies, or evidence of previous injuries should be noted (Table 38.2). Recent studies suggest expanding this examination to include a more detailed evaluation of areas at high risk of injury, such as the knee, ankle, and shoulder.

Laboratory Tests

Routine laboratory screening tests, except for those performed during the general health maintenance visit, are not recommended for the PPE. Screening young athletes for anemia or proteinuria has not been found to be particularly helpful. Such screening may be useful with highly competitive professional athletes, however. Although controversial, some groups believe that electrocardiography and echocardiography should be routine components of the PPE as well.

■ PREPARTICIPATION PHYSICAL EVALUATION

HISTORY FORM

Note: Complete and sign this form (with your parents if younger than 18) before your appointment.

Name: _____ Date of birth: _____

Date of examination: _____ Sport(s): _____

Sex assigned at birth (F, M, or intersex): _____ How do you identify your gender? (F, M, or other): _____

List past and current medical conditions. _____

_____

Have you ever had surgery? If yes, list all past surgical procedures. _____

_____

Medicines and supplements: List all current prescriptions, over-the-counter medicines, and supplements (herbal and nutritional).

_____

_____

Do you have any allergies? If yes, please list all your allergies (ie, medicines, pollens, food, stinging insects).

_____

_____

Patient Health Questionnaire Version 4 (PHQ-4)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Circle response.)

	Not at all	Several days	Over half the days	Nearly every day
Feeling nervous, anxious, or on edge	0	1	2	3
Not being able to stop or control worrying	0	1	2	3
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3

(A sum of ≥3 is considered positive on either subscale [questions 1 and 2, or questions 3 and 4] for screening purposes.)

GENERAL QUESTIONS (Explain "Yes" answers at the end of this form. Circle questions if you don't know the answer.)	Yes	No
1. Do you have any concerns that you would like to discuss with your provider?		
2. Has a provider ever denied or restricted your participation in sports for any reason?		
3. Do you have any ongoing medical issues or recent illness?		
HEART HEALTH QUESTIONS ABOUT YOU	**Yes**	**No**
4. Have you ever passed out or nearly passed out during or after exercise?		
5. Have you ever had discomfort, pain, tightness, or pressure in your chest during exercise?		
6. Does your heart ever race, flutter in your chest, or skip beats (irregular beats) during exercise?		
7. Has a doctor ever told you that you have any heart problems?		
8. Has a doctor ever requested a test for your heart? For example, electrocardiography (ECG) or echocardiography.		

HEART HEALTH QUESTIONS ABOUT YOU (*CONTINUED*)	Yes	No
9. Do you get light-headed or feel shorter of breath than your friends during exercise?		
10. Have you ever had a seizure?		
HEART HEALTH QUESTIONS ABOUT YOUR FAMILY	**Yes**	**No**
11. Has any family member or relative died of heart problems or had an unexpected or unexplained sudden death before age 35 years (including drowning or unexplained car crash)?		
12. Does anyone in your family have a genetic heart problem such as hypertrophic cardiomyopathy (HCM), Marfan syndrome, arrhythmogenic right ventricular cardiomyopathy (ARVC), long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia (CPVT)?		
13. Has anyone in your family had a pacemaker or an implanted defibrillator before age 35?		

Figure 38.1. Preparticipation Physical Evaluation: History Form.

BONE AND JOINT QUESTIONS	Yes	No
14. Have you ever had a stress fracture or an injury to a bone, muscle, ligament, joint, or tendon that caused you to miss a practice or game?		
15. Do you have a bone, muscle, ligament, or joint injury that bothers you?		
MEDICAL QUESTIONS	**Yes**	**No**
16. Do you cough, wheeze, or have difficulty breathing during or after exercise?		
17. Are you missing a kidney, an eye, a testicle (males), your spleen, or any other organ?		
18. Do you have groin or testicle pain or a painful bulge or hernia in the groin area?		
19. Do you have any recurring skin rashes or rashes that come and go, including herpes or methicillin-resistant *Staphylococcus aureus* (MRSA)?		
20. Have you had a concussion or head injury that caused confusion, a prolonged headache, or memory problems?		
21. Have you ever had numbness, had tingling, had weakness in your arms or legs, or been unable to move your arms or legs after being hit or falling?		
22. Have you ever become ill while exercising in the heat?		
23. Do you or does someone in your family have sickle cell trait or disease?		
24. Have you ever had or do you have any problems with your eyes or vision?		

MEDICAL QUESTIONS (*CONTINUED*)	Yes	No
25. Do you worry about your weight?		
26. Are you trying to or has anyone recommended that you gain or lose weight?		
27. Are you on a special diet or do you avoid certain types of foods or food groups?		
28. Have you ever had an eating disorder?		
FEMALES ONLY	**Yes**	**No**
29. Have you ever had a menstrual period?		
30. How old were you when you had your first menstrual period?		
31. When was your most recent menstrual period?		
32. How many periods have you had in the past 12 months?		

Explain "Yes" answers here.

I hereby state that, to the best of my knowledge, my answers to the questions on this form are complete and correct.

Signature of athlete: _____

Signature of parent or guardian: _____

Date: _____

Figure 38.1. Preparticipation Physical Evaluation: History Form. (*continued*)

■ PREPARTICIPATION PHYSICAL EVALUATION

ATHLETES WITH DISABILITIES FORM: SUPPLEMENT TO THE ATHLETE HISTORY

Name: _____ Date of birth: _____

1. Type of disability:	
2. Date of disability:	
3. Classification (if available):	
4. Cause of disability (birth, disease, injury, or other):	
5. List the sports you are playing:	

	Yes	No
6. Do you regularly use a brace, an assistive device, or a prosthetic device for daily activities?		
7. Do you use any special brace or assistive device for sports?		
8. Do you have any rashes, pressure sores, or other skin problems?		
9. Do you have a hearing loss? Do you use a hearing aid?		
10. Do you have a visual impairment?		
11. Do you use any special devices for bowel or bladder function?		
12. Do you have burning or discomfort when urinating?		
13. Have you had autonomic dysreflexia?		
14. Have you ever been diagnosed as having a heat-related (hyperthermia) or cold-related (hypothermia) illness?		
15. Do you have muscle spasticity?		
16. Do you have frequent seizures that cannot be controlled by medication?		

Explain "Yes" answers here.

_____

_____

_____

Please indicate whether you have ever had any of the following conditions:

	Yes	No
Atlantoaxial instability		
Radiographic (x-ray) evaluation for atlantoaxial instability		
Dislocated joints (more than one)		
Easy bleeding		
Enlarged spleen		
Hepatitis		
Osteopenia or osteoporosis		
Difficulty controlling bowel		
Difficulty controlling bladder		
Numbness or tingling in arms or hands		
Numbness or tingling in legs or feet		
Weakness in arms or hands		
Weakness in legs or feet		
Recent change in coordination		
Recent change in ability to walk		
Spina bifida		
Latex allergy		

Explain "Yes" answers here.

_____

_____

_____

I hereby state that, to the best of my knowledge, my answers to the questions on this form are complete and correct.

Signature of athlete: _____

Signature of parent or guardian: _____

Date: _____

Figure 38.2. Preparticipation Physical Evaluation: Athletes with Disabilities Form: Supplement to the Athlete History.

■ PREPARTICIPATION PHYSICAL EVALUATION

PHYSICAL EXAMINATION FORM

Name: _____ Date of birth: _____

PHYSICIAN REMINDERS

1. Consider additional questions on more-sensitive issues.
   - Do you feel stressed out or under a lot of pressure?
   - Do you ever feel sad, hopeless, depressed, or anxious?
   - Do you feel safe at your home or residence?
   - Have you ever tried cigarettes, e-cigarettes, chewing tobacco, snuff, or dip?
   - During the past 30 days, did you use chewing tobacco, snuff, or dip?
   - Do you drink alcohol or use any other drugs?
   - Have you ever taken anabolic steroids or used any other performance-enhancing supplement?
   - Have you ever taken any supplements to help you gain or lose weight or improve your performance?
   - Do you wear a seat belt, use a helmet, and use condoms?
2. Consider reviewing questions on cardiovascular symptoms (Q4–Q13 of History Form).

EXAMINATION		
Height: Weight:		
BP: / (/) Pulse: Vision: R 20/ L 20/ Corrected: ☐ Y ☐ N		
MEDICAL	**NORMAL**	**ABNORMAL FINDINGS**
Appearance • Marfan stigmata (kyphoscoliosis, high-arched palate, pectus excavatum, arachnodactyly, hyperlaxity, myopia, mitral valve prolapse [MVP], and aortic insufficiency)		
Eyes, ears, nose, and throat • Pupils equal • Hearing		
Lymph nodes		
Heart[a] • Murmurs (auscultation standing, auscultation supine, and ± Valsalva maneuver)		
Lungs		
Abdomen		
Skin • Herpes simplex virus (HSV), lesions suggestive of methicillin-resistant *Staphylococcus aureus* (MRSA), or tinea corporis		
Neurological		
MUSCULOSKELETAL	**NORMAL**	**ABNORMAL FINDINGS**
Neck		
Back		
Shoulder and arm		
Elbow and forearm		
Wrist, hand, and fingers		
Hip and thigh		
Knee		
Leg and ankle		
Foot and toes		
Functional • Double-leg squat test, single-leg squat test, and box drop or step drop test		

[a] Consider electrocardiography (ECG), echocardiography, referral to a cardiologist for abnormal cardiac history or examination findings, or a combination of those.

Name of health care professional (print or type): _____ Date: _____

Address: _____ Phone: _____

Signature of health care professional: _____, MD, DO, NP, or PA

Figure 38.3. Preparticipation Physical Evaluation: Physical Examination Form.

■ PREPARTICIPATION PHYSICAL EVALUATION

MEDICAL ELIGIBILITY FORM

Name: _____ Date of birth: _____

☐ Medically eligible for all sports without restriction

☐ Medically eligible for all sports without restriction with recommendations for further evaluation or treatment of

_____

_____

☐ Medically eligible for certain sports

_____

_____

☐ Not medically eligible pending further evaluation

☐ Not medically eligible for any sports

Recommendations: _____

_____

_____

I have examined the student named on this form and completed the preparticipation physical evaluation. The athlete does not have apparent clinical contraindications to practice and can participate in the sport(s) as outlined on this form. A copy of the physical examination findings are on record in my office and can be made available to the school at the request of the parents. If conditions arise after the athlete has been cleared for participation, the physician may rescind the medical eligibility until the problem is resolved and the potential consequences are completely explained to the athlete (and parents or guardians).

Name of health care professional (print or type): _____ Date: _____

Address: _____ Phone: _____

Signature of health care professional: _____, MD, DO, NP, or PA

SHARED EMERGENCY INFORMATION

Allergies: _____

_____

_____

Medications: _____

_____

_____

Other information: _____

_____

_____

Emergency contacts: _____

_____

_____

Figure 38.4. Preparticipation Physical Evaluation: Medical Eligibility Form.

Table 38.2. The 2-Minute Orthopedic Examination

Instructions	*Points of Observation*
Stand facing examiner.	Acromioclavicular joints, general habitus
Look at ceiling, floor, over both shoulders; touch ears to shoulders.	Cervical spinal motion
Shrug shoulders (examiner resists).	Trapezius strength
Abduct shoulders 90°.	Deltoid strength
Full external rotation of arms.	Shoulder motion
Flex and extend elbows.	Elbow motion
Arms at sides, elbows flexed to 90°; pronate and supinate wrists.	Elbow and wrist motion
Spread fingers; make fist.	Hand or finger motion and deformities
Tighten (contract) quadriceps; relax quadriceps.	Symmetry and knee effusion; ankle effusion
Duckwalk 4 steps (away from examiner with buttocks on heels).	Hip, knee, and ankle motion
Back to examiner.	Shoulder symmetry, scoliosis
Knees straight, touch toes.	Scoliosis, hip motion, hamstring tightness
Raise up on toes, raise heels.	Calf symmetry, leg strength

Exclusion Criteria

The most common causes of unexpected death during athletics include undiagnosed cardiomyopathies, anomalous coronary arteries, heart valve defects, primary cardiac rhythm disorders, and pulmonary hypertension. Although most assessments are within reference range, an important part of the PPE is geared toward determining if a patient has risk factors for any of these conditions. Medical exclusion criteria for athletic participation are based on information obtained in the medical as well as family history. Significant historical clues include a family history of sudden, nontraumatic death; premature coronary artery disease in a first- or second-degree relative; a history of palpitations, chest discomfort, or syncope during exercise; and recent, documented infection with Epstein-Barr virus. Controversy exists concerning when athletes can return to collision sports after infectious mononucleosis. A history of a recent or suspected sport-related concussion also requires close monitoring to address when the athlete is cleared to return to participate in a given sport. Current clinical experience and neurocognitive research on adolescents and concussions support the mantra, "When in doubt, sit them out!" In other words, the athlete should not be pressured to continue to play through injuries or return to play on the same day as the injury. Patients with concussions should rest, physically and cognitively, until their symptoms have improved at rest and with exertion, according to the AAP Council on Sports Medicine and Fitness. The exact amount and duration of rest should follow an individualized course because each athlete recovers at a different pace. A stepwise graduated return-to-sport program that was recently updated by the Berlin Concussion in Sport Group allows the athlete to gradually progress through 5 stages a day provided there is no increase in symptoms during exercise. Contrary to previous reports, prolonged inactivity is known to result in a higher symptom level and prolonged recovery. Athletes with more significant injuries, however, may require several weeks to completely recover if the concussion is severe. The short- and long-term effects of sports-related concussions and repetitive head impacts over the life span of athletes of all ages are still under intense investigation in an effort to create appropriate return-to-play criteria and to reduce cognitive, emotional, behavioral, and neurologic consequences.

Findings discovered during the physical examination, such as severe myopia, strabismus, lens subluxation and stature consistent with Marfan syndrome, a cardiac arrhythmia, or the midsystolic click of mitral valve prolapse, could preclude the adolescent from participation in a particular sport. Specific conditions, such as the athlete with 1 kidney, should be evaluated on an individual basis by a physician qualified to assess the safety of the particular sport for the athlete (ie, contact/collision sport vs limited contact sport).

Special circumstances to consider during the PPE are amenorrhea and the female athlete, exercise-induced bronchospasm, anabolic steroid use, and eating disorders that may be associated with certain activities, such as gymnastics, ballet, and wrestling.

CASE RESOLUTION

The young adolescent should first be interviewed with the parent and then alone. Her medical and psychosocial history should be reviewed. A complete physical examination should be performed as well as a pelvic examination if she is sexually active and has a history of lower abdominal pain, abnormal vaginal bleeding, or vaginal discharge. If she is sexually active and asymptomatic or not sexually active, only general laboratory screening tests should be performed and the results reviewed with the patient. The remainder of the visit should be spent discussing issues such as nutrition, exercise, illicit substance use, sexuality and sexual activity, and safety. Results of the physical examination and screening tests should then be discussed with the parent or guardian who accompanied her to the office. If necessary, a follow-up visit should be scheduled. Otherwise, the adolescent should be seen annually.

Selected References

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CHAPTER 39

Health Care for International Adoptees

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CASE STUDY

Jaxon is a 14-month-old boy adopted from Thailand. His biological mother was a 26-year-old commercial sex worker who entered a maternity house during her pregnancy to receive care and relinquish the baby for adoption. His mother reported that she was physically and sexually abused as a child and became a street child at age 14 years. She used illicit drugs 5 years previously but none since. She identifies the father as a European customer but has no other information. Jaxon was born at 32 weeks' gestational age and was placed in an incubator but did not have any respiratory problems. He has been in foster care in the home of a Thai family with his care supervised by an internationally respected adoption organization. He was selected by his parents at the age of 4 months, and they have received monthly progress reports on his growth, development, and medical status. Reportedly, he has had several "colds" and 1 ear infection but otherwise has been growing and developing well. Before departure to pick up Jaxon, his adoptive parents met with you to prepare for his arrival.

The parents placed a call to you from the Bangkok airport because Jaxon would not stop crying. They report that on the morning his foster mother left him with them, he cried quite a bit but had settled by bedtime and seemed to be adjusting well during the week. Over the 12 hours preceding the telephone consultation, however, he had not stopped crying, and he refuses to eat. He has been drooling, and they question if his discomfort is related to teething; they have not noticed any other symptoms of teething, however. They are gravely concerned that he does not like them and is having attachment difficulties.

Questions

1. What factors influence the prevalence of international adoption?
2. What are some of the potential health problems of the international adoptee?
3. What is an appropriate medical evaluation for the international adoptee?
4. What is the role of the pediatrician in caring for the child and newly formed family?

Although internationally adopted children come from a wide range of birth countries, many of their health-related issues are similar. Many of the children have lived in orphanages in impoverished areas of the developing world and have incurred the maladies associated with poverty and deprivation.

Epidemiology

From 1999 to 2012, 242,602 children were adopted internationally into the United States; this is nearly the same number as the previous 30 years combined. Through the first decade of the 21st century, 90% of such children were from Asia, most commonly China and South Korea; Eastern Europe; and South America (Guatemala and Colombia). From 2009 to 2012, China, Ethiopia, and Russia were the 3 leading countries of origin for children adopted into the United States. The number of international adoptions has been declining since 2009, with a nadir in 2017 of only 4,714 adoptees entering the United States. This decline is the result of multiple factors, including economic uncertainty in the United States; changing geopolitical landscapes in birth countries; and stricter policies governing adoption in an attempt to curb corruption, including The Hague Convention on the Protection of Children and Co-operation in Respect of Intercountry Adoption, which is an international agreement for standardizing intercountry practices to promote protection of children available for adoption.

Many factors influence the choice of international adoption. In the United States, delays in childbearing and associated infertility have increased the demand for adoptable children. Simultaneously, more readily available birth control and growing acceptance of single motherhood have resulted in a decreased number of infants available for adoption. In addition to the shortage of adoptable children in the United States, other factors in the decision to pursue international adoption include real and perceived risks of domestic adoption (eg, failure of birth parents to relinquish rights), reluctance to adopt a child with special needs or with in utero drug exposure, and limited availability of children with desired traits (eg, specific age and ethnicity [often white infants]). The prompt termination of rights of birth parents in international adoption is also cited as a factor in this decision.

The advent of intercountry adoption in the United States occurred in conjunction with World War II and the large number of orphaned children in Europe, many of whom were fathered by American soldiers. The second—and more formalized—wave of intercountry adoption occurred with the Korean War. Because of the need to care for unwanted orphans, primarily of mixed ethnicities and fathered by American soldiers, South Korea established a foster care system and the children became available for adoption to Americans. War and political turmoil remain factors in the availability of children for adoption. For example, the fall of communism was a significant factor in Russia and other states of the former Soviet Union becoming common birth countries for adoptees in the 1990s and the early part of the 21st century. Following a diplomatic rift, however, in 2013 the Russian government outlawed adoptions to the United States. Early in the 21st century, because of poverty and political strife, more children were being adopted from African countries, especially Ethiopia. Recently, adoptions from Ethiopia have been stopped, however, in part because of cultural pride, as well as a highly publicized death resulting from abuse of an Ethiopian child adopted into the United States.

Societal values also influence adoption practices. China was among the leading birth countries for adoptees because of the population control initiatives of the government mandating that families have only 1 child. With this practice and the desire for a male heir, some newborn girls were abandoned and became available for adoption. With the 2008 Summer Olympic Games, China had a surge in national pride and a realization that their future population may not include enough girls for the boys to marry. Subsequently, fewer infant girls became available for adoption. Currently, China mainly permits international adoption of children of both sexes with special medical or developmental needs.

Until 2016, most internationally adopted children were female (approximately 56%), in part reflecting the adoption of girls from China, as well as a preference among some adoptive parents (especially single women) to adopt a girl. Currently, most are male, mainly reflecting the changes in China's policies. International adoptees are young, with approximately 55% between the ages of 1 and 5 years.

The United States is the birth country of approximately 100 children annually adopted into other countries. Absolute statistics for US children adopted into other countries are not available because the US government does not routinely report the number of exit visas issued for adopted children. These adoptees are often males of African American or mixed ethnicity and are adopted by families in Canada and Western Europe. They are available purportedly because of the low desire for these infants by adoptive parents in the United States.

The status of the country of origin (eg, war, turmoil, poverty, societal values) aside, significant overlap exists in the reasons that children from foreign countries and from the United States become available for adoption. The common reasons include parental substance use, abandonment, chronic neglect, abuse, and domestic violence, all of which often are associated with underlying poverty.

Until the 1990s, most international adoptees were from South Korea, which had in place an excellent foster care system and health care. Since the 1990s, most adoptees come from institutions in poor nations without a developed foster care system, resulting in a significant decline in the health and well-being of adoptees.

Clinical Presentation

Preadoption

Some adoptees become known to the US health professional "only on paper" during the preadoption stage. The adoptive parent or parents may ask their physician for help in assessing the child's medical status. Often a parent receives a written health report (varying in the quantity and quality of information) and photos or videos of the child under consideration for adopting. The written documents may be in a foreign language or not translated by an experienced medical translator. Because some countries prohibit international adoption of healthy children, diagnoses may be embellished to improve the child's chances for adoption. Additionally, some medical records contain diagnoses that are nonsensical in US medicine but represent standard terms used in the country of origin. These inconsistencies are quite challenging when trying to evaluate the medical records of potential adoptees. Many physicians may not feel comfortable with reviewing medical records given so many limitations; however, even with all the caveats, review of the records may provide valuable insight into the health status of the adoptee.

During this stage, the physician may provide information for parents and families for preventive health measures to prepare for travel to a developing area of the world. The Centers for Disease Control and Prevention (CDC) Traveler's Health website (www.cdc.gov/travel) is a good resource for physicians and parents. Up-to-date information may also be obtained from the World Health Organization (WHO) and the US Department of State (Table 39.1). Prospective parents should be informed about the infections that may occur in international adoptees, and they should receive appropriate education and preventive measures, including vaccinations (eg, measles, hepatitis A, hepatitis B).

During the Adoption Trip

All internationally adopted children are required by the US Department of State to undergo a physical examination before admission into the country; however, this examination is limited in scope and performed mainly to rule out severe impairments or certain communicable diseases that may pose a public health threat (eg, active tuberculosis [TB]). This examination should not be considered a complete medical evaluation for an individual child.

Some health professionals can provide support for families during travel via e-mail, telephone, and the internet, similar to telephone consultations performed in general practice.

Postadoption

After the adoption, the health status of children on presentation to the US physician may be quite variable, ranging from well to severely

Table 39.1. Websites With Information on International Health, Travel, and Adoption

Resource	*Information*	*Website(s)*
Centers for Disease Control and Prevention	Up-to-date information for travelers' health Health guidance and immigration process for international adoption	wwwnc.cdc.gov/travel www.cdc.gov/immigrantrefugeehealth/adoption/index.html
US Department of State	Up-to-date information for travelers' risk (eg, civil unrest) Intercountry adoption procedures	https://travel.state.gov/content/passports/english/alertswarnings.html https://travel.state.gov/content/travel/en/Intercountry-Adoption/Adoption-Process.html
World Health Organization	Health status and recommendations for immunizations for each country Assists with interpreting foreign vaccine records	www.who.int/immunization/policy/immunization_tables/en/
US Department of Health & Human Services Administration for Children & Families	Adoption information and procedures	www.childwelfare.gov

ill with acute infections or chronic diseases (eg, malnutrition, TB). The adopted child should be seen by the physician within 2 to 3 weeks of arrival in the United States, or sooner if the child has an acute illness. This 2-week period allows for the child (and parent or parents) to recover from jet lag and become more familiar with each other, permitting a better assessment at the visit. If an acute illness visit is required, a separate appointment for a comprehensive evaluation should be scheduled at a later time.

Health Care Issues

In addition to problems commonly related to poverty and deprivation, many health issues are specific to the country or region of origin (eg, increased risk of malaria and other parasites in children from the continent of Africa). Adoptees from South Korea have the lowest risk for infectious diseases.

Generally, health care issues for adoptees are extensive, including acute illness (eg, respiratory infections), chronic illness (eg, anemia, malnutrition, poor dental hygiene, TB, asthma, parasite infestation), delayed or unknown immunizations, psychosocial challenges, and impaired growth and development.

Some children have assigned birth dates (eg, abandoned infants and street children for whom birth dates are not known), and they may have small growth parameters, making it difficult to know their true age and expected development. Developmental delays, most commonly language delay, are frequently identified. Assessment of development may be even more difficult in infants and young children who are nonverbal and older children who speak their native language.

Growth delay is common for adoptees. Many children are malnourished or exhibit failure to thrive, and these conditions are often multifactorial in origin, including poor prenatal environment (eg, maternal stress, malnutrition, substance abuse), inadequate calories, inadequate nurturing, unrecognized genetic or congenital disorders (eg, fetal alcohol spectrum disorder; see Chapter 147), and untreated chronic illness (eg, TB, rickets). Institutionalized children may exhibit psychosocial dwarfism and may lose 1 month of linear growth for every 3 to 4 months spent in the orphanage. Delay in puberty may be observed in adolescents from deprived environments, such as orphanages. Precocious puberty may also be seen among international adoptees.

Immunization records may not be available, may be incomplete, or may be in a foreign language, which hinders assessment of the vaccination status of adoptees. Many vaccines available in the United States are not available in the developing world (eg, *Haemophilus influenzae* type b, pneumococcal conjugates) and, thus, children will not have had them. Adopted children immigrating to the United States who are younger than 10 years are exempt from the Immigration and Nationality Act regulations requiring proof of immunizations before arrival; however, adoptive parents are required to sign a waiver that they will comply with US recommended immunizations after arrival.

Psychosocial, emotional, and mental health disorders are some of the more challenging problems to assess. The spectrum of mental health problems is related to age and previous life experiences of the child. Children may have experienced physical or sexual abuse before placement in an institution, and they may also be subject to abuse by older children or adult caregivers while in institutional placement. Attachment disorders are among the most concerning abnormalities for adoptive parents, adoption professionals, and health professionals. The fundamentals for learning healthy attachments are greatly influenced by early infant-caregiver relationships. Thus, many international adoptees have difficulties bonding, in part because they have not had secure caregiver relationships. Issues of attachment and bonding may be especially problematic for children who have resided in an orphanage or had multiple caregivers from an early age. Children who have had multiple caregivers may be indiscriminately friendly, which may pose risks for their safety. Other common mental health problems include depression,

attention-deficit/hyperactivity disorder, posttraumatic stress disorder, abnormal behaviors (eg, self-stimulating behaviors, hoarding food, sleep disturbances), and oppositional defiant disorder. As mentioned previously, communication with the child may be difficult because of language barriers, causing another obstacle to assessing the child's mental health.

Sensory integration difficulties are increasingly recognized in adoptees. The children may have adverse responses to touch (eg, new clothing, hugs and kisses, bathing) or textures (eg, new foods). Individual senses or all of them (ie, hearing, vision, taste, smell) may be notably increased or decreased, and some children have decreased sensation to physical pain, resulting in an increased risk for injuries. Dyskinesia in the form of clumsiness or being prone to injury has also been observed.

The most common identified medical issues are infectious diseases, including acute illness (eg, upper respiratory infection, bronchitis, otitis, infectious diarrhea) and chronic infection (eg, TB, parasite infestations, with scabies and *Giardia lamblia* common manifestations of the latter. Because of the lifestyle of their biological mother and the children's time residing in institutions, many adoptees are at increased risk of exposure to infectious diseases, such as syphilis, HIV, and hepatitis B and C.

Preventive care that is considered routine in the United States is unlikely to have been part of the child's care and must be performed as appropriate for age. This includes newborn screening laboratory studies and assessments of hearing, vision, dental, and mental health. Anticipatory guidance for new parents should be incorporated into preadoption encounters and all subsequent visits.

Evaluation

The initial office visit with the physician should be scheduled for an extended period because of the complexity of the evaluation and additional time needed for parental education. If the physician's schedule does not permit extended visits, ancillary staff (eg, nurses, dietitians, therapists) may perform parts of the evaluation and education.

Observation of the child's behavior, development, and interactions with the adoptive parent or parents and physician is a critical element of the evaluation. Most physicians routinely include such observations in their visits, but particular attention to these factors is necessary for new adoptees. Items to notice include the child's demeanor and behavior, such as determining whether the child is easily engaged or is withdrawn, makes eye contact with the parent or physician, makes any vocalizations or words (depending on the child's age), plays with toys, is too friendly or is afraid of strangers, and seeks comfort from the new parent or parents.

History

Limited medical information is available from most birth countries, although some exceptions exist (eg, from foster care in South Korea). Family and birth history are rarely obtainable for adoptees. Immunization histories are becoming increasingly available. Previously, vaccine records were considered unreliable; however, in recent years, data have emerged to suggest that well-documented immunizations may be considered valid. Written records showing the age of the child when vaccinated, date of administration, dose given, and proper intervals between dosing that are consistent with WHO schedules or are comparable to US schedules may be considered acceptable for proof of immunization. (Guidelines for care in the absence of vaccine records is discussed in the Management section of this chapter.)

Dietary history is important for assessing the child's nutritional status. Questions to ask are listed in Box 39.1.

An interim medical history may be available, because many children are selected by their adoptive parent or parents several months before immigrating to the United States. The interim medical history may be provided from the orphanage or foster care provider through the adoption agency. Parents should be encouraged to solicit as much information as possible from the child's caregivers. At a minimum, this history should include serial growth parameters, known illnesses, hospitalizations, surgeries, allergies, and immunizations given while the child was under their care. Parents should also ask caregivers about any food preferences, special fears, toys, or friends from the placement prior to adoption. If the child has a special "lovey," the parent or parents should request to bring it with the child as a transitional object.

Physical Examination

A complete unclothed physical examination should be performed on infants and children of all ages. Because of previous trauma (eg, sexual abuse), however, it may be necessary to perform some parts of the examination over a series of visits to minimize the possibility of inflicting additional trauma from an examination. All aspects of the physical examination are essential. Accurate measurements of height, weight, and, depending on age and size, head circumference should be obtained. Plotting of parameters on the growth curves from WHO or the CDC (compared with birth country) should be used, with few exceptions. The child should be closely inspected for unusual scars or bruises, evidence of fractures (old or recent), rachitic changes, and genital or rectal scarring. The skin should be examined for rashes, lesions, and a bacille Calmette-Guérin (BCG) scar (typically on the upper deltoid). Developmental screening should be performed, and a more complete developmental assessment should be scheduled at a separate visit (when the child is not distressed or acutely ill). A dental examination should be included, and referral for a formal dental

Box 39.1. What to Ask

Dietary History of the International Adoptee

- What food and formula/milk is the child receiving?
- Has the child received adequate calories?
- Is there known or suspected food intolerance? (For example, lactose intolerance is more common in Asian ethnicities.)
- Are there abnormal behaviors associated with food or eating (eg, preoccupation with food, hoarding, food refusal, gorging)?

evaluation likely will be necessary. Screening evaluations of hearing and vision should be performed; formal testing may be necessary, depending on the age of the child and ability to cooperate.

Laboratory Testing

Laboratory studies should include complete blood cell count, lead levels, and thyroid function testing (iodine is not in many diets in Asia) (Box 39.2). Additionally, testing for illnesses associated with specific countries of origin, findings on examination (eg, comprehensive metabolic panel for malnourished child), and as directed by the child's age (eg, newborn screening for metabolic disorders in newborns and infants) should be performed. Screening tests, if initially negative, should be repeated in 3 to 6 months, especially for children for whom concerns exist about underlying malnutrition or of immunocompromised status.

Because of the increased risks of exposures, laboratory screening for infectious diseases should be undertaken. Serum samples should be tested for syphilis (nontreponemal and treponemal antibodies), hepatitis surface antigen B panel (HBsAg, HBsAg antibody [HBsAb], and hepatitis B core antibody), hepatitis C antibody, and HIV 1 and 2 antibodies. Human immunodeficiency virus polymerase chain reaction may be indicated in some children (eg, those who may not make specific antibodies because of malnutrition or immunocompromised status). Stool samples should be sent for ova and parasite examination and *Giardia* and *Cryptosporidium* antigen testing (Box 39.2). Stool for bacterial pathogens (eg, *Salmonella, Shigella*) should be sent from children from some regions, such as the Indian subcontinent. Because cytomegalovirus infection is ubiquitous, routine testing is not recommended. Testing for acute infection with hepatitis A virus (HAV) by measuring immunoglobulin M anti-HAV antibodies should be performed for adoptees from HAV-endemic areas, because infants and young children may be asymptomatic but contagious. Administering HAV vaccine, as recommended in the United States, is not problematic for children who may have had previous HAV infection.

Tuberculin skin testing (ie, purified protein derivative [PPD]) should be performed on all children; history of receipt of BCG is not a contraindication to skin testing. Bacille Calmette-Guérin vaccinations usually are given at birth in most developing nations, and its influence on skin test status is controversial. Generally, BCG given within the previous 1 to 2 years may contribute to a positive PPD skin test; however, a positive PPD test is more likely reflective of true infection with *Mycobacterium* with or without active disease and merits further evaluation. For children 5 years and older, interferon-γ release assays (eg, QuantiFERON-TB Gold) are an acceptable screening alternative to PPD testing. Latent TB infection has been reported in 0.6% to 30% of international adoptees, which is not surprising because most adoptees come from areas in which TB is endemic.

Box 39.2. Recommended Laboratory Testing for International Adoptees

- Hepatitis A IgM.
- Hepatitis B virus serologic testing.
  - Hepatitis B surface antigen
  - Antibody to hepatitis B surface antigen
  - Antibody to hepatitis B core antigen
- Hepatitis C virus serologic testing.
- Syphilis serologic testing.
  - Nontreponemal test: RPR, VDRL, or ART
  - Treponemal test (MHA-TP or FTA-ABS)
- HIV 1 and 2 serologic testing.
- Complete blood cell count with differential and red blood cell indices.
- Stool examination for ova and parasites (3 specimens).
- Stool examination for *Giardia intestinalis* and *Cryptosporidium* antigen (1–3 specimens).
- Additional parasite testing.[a]
  - *Trypanosoma cruzi* serology if child is from endemic area
  - If child has eosinophilia (eosinophil count >450 cells/mm^3 with negative ova and parasite stool testing): *Strongyloides* serology and *Schistosoma* serology if from endemic area
- Tuberculin skin test.[b]
- Consider antibody testing to select vaccine antigens (if written records are unreliable).[c]
- Additional testing: thyroid function tests, lead level, and others as directed by history and physical examination (see text).

Abbreviations: ART, automated reagin test; FTA-ABS, fluorescent treponemal antibody absorption; IgM, immunoglobulin M; MHA-TP, microhemagglutination test–*Treponema pallidum*; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories.

[a] In conjunction with international adoption or infectious diseases specialist.

[b] Repeat at 6 months after initial testing.

[c] For children older than 6 months, may check diphtheria, tetanus, and polio; for children older than 12 months, may check measles antibodies.

Derived from the American Academy of Pediatrics and the Centers for Disease Control and Prevention.

Management

Counseling for the Transition

Education and preparation for the parent or parents and all family members is a priority. Generally, countries of origin for adoptees are in the developing world, and parents should prepare for healthy travel for themselves by receiving immunizations and following travel guidelines from the CDC and the US Department of State.

Parents should provide consistent structure and boundaries in a loving milieu for adoptees. A scheduled regimen may be especially important to previously institutionalized children because it has been their way of life, but even children who were not institutionalized benefit from a predictable routine. Parents should maximize their 1-on-1 interactions with their adoptee while still allowing time for themselves and other family members—not an easy task with multiple children. Initially, it may be necessary to temper physical contact and affection as directed by the child's tolerance. Parents should try to enhance bonding and attachment by frequently identifying themselves as "Mom" or "Dad." Other strategies to enhance attachment include initially limiting contact with individuals outside

the family and not "handing" the child to others, including non-household family members, because they are strangers to the child. Frequent verbal reassurances and talking to the child about the people and the new world around the child should be encouraged. In caring for the child, the parent or parents should be encouraged to meet the child at the child's developmental level rather than chronologic age.

Growth and Nutrition

When children are identified as malnourished or exhibiting failure to thrive, a multidisciplinary treatment plan is recommended, including the parent or parents, physician, nutritionist, and therapists (eg, occupational therapist for feeding difficulties). The child should be offered familiar foods, if that is the child's preference, and each meal may include a new, more nutritional offering. Children should be offered frequent meals and snacks, because they may not be able to eat much at a single sitting. Foods should be calorie dense and, depending on the child's age and previous dietary history, may include foods such as added butter, cheese, avocado, and peanut butter. Dietary supplements, such as PediaSure or Boost, may be indicated.

Precocious puberty has been observed more in female international adoptees than male international adoptees and is thought to be related to the rapid improvement of nutrition. If signs of precocious puberty are observed, evaluation by a pediatric endocrinologist is recommended.

Development

Because developmental delays are so common among international adoptees, most of them should undergo developmental assessment. Language delays, especially expressive delay, are common; when any such delay is identified, formal audiology testing should be included in the assessment. Performing developmental assessments of language poses difficulties, however, because most are conducted in English, which is rarely the child's primary language. Repeating the testing after a period of adjustment may be helpful. Language barriers do not preclude audiology testing.

Mental Health

Mental and emotional health problems are common and may manifest early or late or occur as relapses. Initial problems may include sleep disorders, fears and phobias, bizarre behaviors, and self-stimulating behaviors. Unless the behaviors pose a safety risk, parents should tolerate them because most dissipate with time in a secure environment. At times of emotional distress, parents may observe a relapse of behavior problems. For milder disorders, physicians may provide guidance to parents; however, moderate and severe disorders merit prompt referral to a mental health professional, ideally someone with expertise in adoption.

Immunizations

If vaccinations are considered valid, as described previously, resuming immunizations per the US schedule (see Chapter 37) is appropriate. If immunization status is unknown or incomplete, however, repeating immunizations or checking antibody concentrations to vaccine antigens is an acceptable option. Most areas of the world routinely administer BCG, polio (oral), and vaccines containing diphtheria and tetanus toxoids with pertussis (often whole-cell) components. Receipt of additional diphtheria, tetanus, and possible pertussis antigens may be associated with an increased risk of adverse events; measuring antibodies to diphtheria and tetanus is warranted to minimize the risk of adverse events. No US Food and Drug Administration–approved antibody tests are available commercially for pertussis antibodies. Receipt of additional doses of inactivated polio vaccine is not usually associated with adverse events. Testing for HBsAb should be performed on all adoptees, and planning for further immunizations will be based on these results. Hepatitis B vaccine will elicit only HBsAb responses; the presence of antibodies to other hepatitis B antigens is suggestive of natural infection. For measles, mumps, and rubella, various formulations and combinations (1- and 2-component more commonly than 3-component) vaccines are available worldwide. Checking antibodies to these antigens is possible, but it likely may be necessary to administer a US-licensed combination (eg, measles, mumps, and rubella) to ensure protection against all 3 antigens. Most of the other vaccines available in the United States are not available in the developing world (eg, *H influenzae* type b, pneumococcal conjugates, varicella, HAV), and the child should receive these vaccines as recommended for age per the US schedule.

Infectious Diseases

Any acute identified infectious disease (eg, scabies, otitis) should be managed following standard practice, bearing in mind the possibility that different antibiotic resistance patterns exist in other parts of the world. Thus, if the child does not have the predicted response to treatment, consultation with a pediatric infectious diseases specialist should be considered. For other infectious disease screening noted previously, additional evaluation and possible management should be initiated promptly (eg, penicillin therapy for syphilis) and pediatric infectious diseases consultation may be considered.

For TB evaluation, any positive PPD skin testing merits further investigation for true infection with *Mycobacterium tuberculosis.* A compounding problem is that some children may be anergic resulting from malnutrition, and a false-negative PPD test result may be obtained. If malnutrition is suspected, obtaining a chest radiograph should be considered even if the PPD is negative, and consideration should be given to repeating the PPD when the child's nutritional status has improved. Additionally, routinely repeating the PPD 6 months after the child's arrival is advisable if the child is from an endemic area, because late exposure to an infected individual is possible.

Prognosis

Being prepared for the complex needs related to international adoption has been identified as the best determinant for parents to consider the adoption experience as positive, regardless of the number or severity of the medical needs of the adoptee.

With improved nutrition and environment, most children have significant catch-up growth; however, up to one-third of adoptees may have unrecoverable loss in linear growth. In terms of intellectual development, by 1 year of age nearly all children in orphanages have 1 or more areas of delay. Their prognosis is generally good, however, with an increase in 2 developmental quotient points per month after arrival in the United States. For children who have been in an orphanage for the first 3 years after birth, the longer the time of subsequent institutionalization the greater the negative effect on IQ and development.

Many children have ongoing mental and psychosocial problems, and some disorders do not manifest until children are older, such as attention-deficit/hyperactivity disorder or learning disorders when the child is of school age. Ongoing attachment disorders seem to occur with greater frequency in children with lower IQs and more behavior problems than average as well as in adoptive families of a lower socioeconomic status.

Assessment of the overall outcome of children who spent 8 or more months in institutional care in Eastern Europe, when evaluated at least 3 years after adoption, showed that approximately one-third had multiple serious problems, including IQ less than or equal to 85, insecure attachment, and severe behavior problems; approximately one-third had a few serious problems but were thought to be making progress; and approximately one-third had progressed very well. The best predictors of major problems were greater length of time in the orphanage, increased number of children adopted at the same time, younger adoptive mother, lower socioeconomic status of mother, and father alone selected the child. Although the effect of these risk factors may not be identical for all birth countries, they do provide some insight. Reviewing these risk factors with adoptive parents during the preadoption period may aid in their decision making.

Role of the Pediatrician

The role of the pediatrician is not to tell the adoptive parent whom to adopt; parents are essentially choosing life partners, which is an individual decision. The pediatrician can, however, assist the parent or parents in reviewing available medical information, which may help the parent or parents make an informed decision about proceeding with an adoption.

During the adoption process, the physician must assume an active role as a child advocate as well as parental advocate and educator. This may be the first parenting experience for the adoptive parent or parents and, thus, education on the basics of child care is necessary, no matter the age of the adoptee. This might include feeding and routine care (eg, estimate the number of diapers needed if traveling to an area with no access to supplies), as well as discipline techniques for a traumatized child. It is necessary to be prepared to care for illnesses because many adoptees are ill at the time of the adoption and travel. The parent or parents may be isolated from their usual support systems while embarking on the new role of parent, and the pediatrician can facilitate emotional preparation for that experience.

After the family returns home, the pediatrician has a role as primary care provider and in serving as a referral source for specialty care, such as in medical subspecialties, mental health, postadoption support services, developmental intervention, and nutrition.

Counseling Adoptive Parents About Expectations

Parents should be informed that it is unlikely that an institutionalized child will emerge from such a situation unscathed. Bearing this in mind, parents may make preliminary preparations for treatment and rehabilitation for the child. Families should be counseled that it is acceptable to say "no" to a potential adoptee. No one benefits from adoption of children by families who do not have the necessary resources to care for them. Most importantly, parents should be reassured that optimism is appropriate. Being prepared matters!

CASE RESOLUTION

In the telephone consultation, the parents report that they have not observed any injuries and no areas seem tender when they examine Jaxon, per your suggestion. They elect to give him some diphenhydramine and fly home with the plan to make an office visit on arrival. Although they are exhausted, they travel directly to your office for an acute care visit. They report that Jaxon remained inconsolable and that the flight home was miserable for him and everyone around them. On entering the examination room, Jaxon was screaming and noticeably uncomfortable but trying to find comfort in his father's arms.

His temperature was 38.9°C (102°F) axillary, his pulse rate was 144 beats per minute, and his respiratory rate was 30 breaths per minute. His examination was notable for extensive oral and pharyngeal vesicular lesions with erythema, but he had no labial lesions. He had multiple shotty cervical nodes, and the rest of the examination was noncontributory. A diagnosis of herpangina was made. He was given a dose of ibuprofen, and 15 minutes later he was quiet, able to swallow electrolyte solution, and cuddling in his father's arms. His parents were reassured that this was an acute infection and not an indication of poor bonding; in fact, Jaxon was already seeking comfort from them. Additional testing for infections included obtaining antibodies to HIV, rapid plasma reagin for syphilis, and hepatitis C and hepatitis B panel, which was especially important because of his biological mother's history of being a commercial sex worker. Other testing included complete blood cell count, lead level, and thyroid function. An appointment was made for 2 weeks hence to complete the assessment, including a developmental assessment; this evaluation was deferred because he was acutely ill at the time of the initial office visit.

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CHAPTER 40

Health Care Needs of Children in Foster Care

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CASE STUDY

A 13-year-old girl is brought to your office by her foster parent for a general physical examination. The foster parent states that the girl has been living in her home for the past 2 weeks. When the child was initially brought by the social worker, she was wearing dirty clothes and smelled of cigarette smoke. Neither medical records nor immunization records are available for your review, and the teenager is not sure the last time she saw a doctor. The girl states that she often missed school to help care for her sick grandmother. She gets very quiet when you ask about her family. She states that she misses her younger sisters but does not mention anything about her mother. When asked about her mother, she states that she does not care to see her because her mother "cares more about her boyfriend than she does me and my sisters." The only history known by the foster parent is that the child was failing school because of frequent absences and that there were extensive amounts of pornography and drug paraphernalia found in the home at the time of removal. The social worker also told the foster mother that an expired albuterol inhaler was found in the home with the girl's name on it. The foster parent states that the teenager seems "sad" all the time, and 2 nights previously when asked about school, she began to cry and ran to her room.

On physical examination, the patient is sad appearing and quiet, but cooperative. Her weight is in the 25th percentile and her height is in the 50th percentile for her age. She has poor dentition with multiple dental caries. She has a few basilar wheezes on lung examination and has scattered bruises on her anterior shins; no other abnormalities were noted.

Questions

1. What are the medical, psychological, and behavioral issues that commonly affect children in the foster care system?
2. What is the role of the primary care pediatrician in providing a medical home for the child in foster care?
3. How does a child's legal status as a child in foster care affect how medical care can be delivered?
4. What are the appropriate health care referrals and community resources to access for a patient who is in foster care?

The term *foster care* refers to the temporary placement of a child in the home of another caregiver or foster parent because of a threat to the child's safety or well-being in the original home. Placement of a child in foster care results from an investigation of the child's home environment by child protective services (CPS) and may be arranged via voluntary agreement of the parent or through court sanction. The foster parent may be related to the child (also known as kinship care) or may be a nonrelative. For children in voluntary placement, the biological parent retains the right to terminate the placement at any time. For those placed by legal sanction, a series of court hearings give parents, the child, and the CPS agency the opportunity to present their perspectives on the circumstances surrounding the allegations as well as their respective views on interventions to ensure the child has the best home environment.

Children in foster care may present to the primary care pediatrician soon after placement in foster care or after living with a foster parent for a long time. In either scenario, children in foster care often have a significant number of unmet medical and mental health needs because of complex psychological trauma and limited access to health care. These children have rates of medical and mental health disorders that are higher than those of children from equivalent socioeconomic backgrounds who are not in foster care. Thus, foster children should be considered part of the special needs patient population.

At the time of initial removal, the CPS worker may not be able to obtain a medical history or essential information about current medications for the child. Changes in foster care placement may interrupt continuity of care with a health professional, and frequent changes in assigned social services caseworkers can create barriers to communication among biological parents, foster parents, health professionals, and caseworkers.

Traditionally, those in the general medical community have lacked an appreciation for the complexity of the needs of this patient population. Additionally, in part because of low payment rates, it

has been difficult to allot sufficient time in a "routine" office visit to complete the comprehensive evaluation these children require. For those children with identified mental health needs, often few psychiatric and psychological resources are available; this is particularly true for children younger than 5 years.

These unmet needs have long-lasting effects on the well-being of the children, even after exiting the foster care system, including into adulthood. Data have shown that the more adverse childhood experiences to which a child is exposed (eg, abuse, neglect, parental substance abuse, witnessing domestic violence; see Chapter 142), the higher the risk for heart disease, suicide, obesity, and other conditions in adulthood, including early death.

Because of their complex health care issues and vulnerability to fragmented care and adverse childhood experiences, foster children merit a medical home that provides comprehensive, multidisciplinary services and medical case management.

Epidemiology

At any point during a given year, 600,000 children in the United States spend time in foster care. Approximately 275,000 children enter the system annually. Reasons for placement, in descending order of prevalence, include neglect, physical abuse, psychological or emotional abuse, and sexual abuse. As a population, children in the foster care system come from home environments that experience high rates of poverty, parental mental illness, parental substance abuse, unemployment, adolescent parenthood, frequent involvement with the criminal justice system, and low levels of education. Foster children have high rates of exposure to domestic violence, and many are victims of neglect, physical abuse, and sexual abuse. Their biological parents often have limited parenting skills; the children experience inconsistent parenting behaviors along with minimal developmental stimulation and emotional support. All these factors combine to cause unpredictable, stressful, and unsafe home environments for these children, prompting their removal and placement into foster care. Children in foster care account for 25% to 41% of Medicaid expenditures despite representing less than 3% of all enrollees.

Foster children are of all ethnicities, but children of color are disproportionately represented. Children younger than 5 years comprise nearly one-half of the children in foster care, with those 11 to 15 years of age a distant second. In the past several decades, an increasing percentage of new entrants into foster care are infants younger than 1 year of age. Many of these infants are exposed to substances prenatally and are placed in foster care because of a combination of factors related to maternal drug use.

Approximately 70% of children leave foster care within 2 years of placement, with the average stay being 20 months. More than one-half of these children are reunited with their biological parent or primary caregiver. Six percent remain in foster care for more than 5 years, and approximately 35% of all children who leave foster care later reenter the system because of a new CPS report. Since the 1990s, the number of adoptions from foster care has increased to 20% of those leaving the child welfare system. An additional 8% of those leaving foster care emancipate out of the system by reaching 18 years of age without attaining permanent placement. Many of these teenagers later report being incarcerated or homeless at some point after emancipation. Twenty-five percent of the children in foster care will experience 3 or more placements, which results in further fragmentation of their health care and education. Multiple foster care placements are more common for those children with behavioral, emotional, or coping problems.

Clinical Presentation

Medical Issues

Children in the foster care system have been shown to have high rates of acute and chronic illness at the time of their initial medical evaluations after placement (Box 40.1). Thirty percent to 80% of children entering foster care have at least 1 medical concern, with one-third having a chronic illness. Common conditions include obesity, asthma, vision or hearing problems, neurologic disorders, gastrointestinal diseases, dental caries, and other inadequately managed chronic illnesses, such as eczema and anemia. Acute infections are also common, including respiratory tract infections, skin infections, otitis media, sexually transmitted infections (STIs), and intestinal infestations with parasites. Low immunization rates are a frequent occurrence.

Many children entering foster care have growth delay, with weight, height, or head circumference measurement less than the 5th percentile for their age. This may be caused by a combination of factors, including inadequate nutrition, environmental deprivation, prenatal alcohol exposure, genetic predisposition, and underlying illness (eg, HIV infection). Behaviors such as rumination and social withdrawal may manifest in children in environments that are chronically stressful or lack the necessary stimulation and support for a child. (For further discussion of failure to thrive, see Chapter 146.) Overweight (ie, body mass index [BMI] 85%–95% for age) and obesity (ie, BMI >95%

Box 40.1. Medical, Developmental, and Mental Health Issues Common to Children in Foster Care

- Acute infection
- Undiagnosed or inadequately treated chronic illness
- Dental caries
- Growth delay and failure to thrive
- Incomplete immunization history
- Prenatal or perinatal exposure to sexually transmitted infection
- Effects of prenatal substance exposure
- Physical sequelae of physical and sexual abuse
- Developmental delay
- Attention-deficit/hyperactivity disorder
- Posttraumatic stress disorder
- Anxiety
- Depression
- Conduct and oppositional defiant disorders
- Attachment disorders
- Educational disabilities

for age) are also common among children in foster care. Depression, dysfunctional coping skills, and lack of family connectedness also contribute to suboptimal health.

Many children placed in foster care have a history of prenatal exposure to illicit drugs, alcohol, and tobacco. These children have high rates of preterm birth and prenatal or perinatal exposure to infections such as hepatitis C, hepatitis B, HIV, syphilis, and herpes simplex. This risk of exposure to infectious agents is related to maternal drug use and its frequent association with prostitution, needle sharing, and drug use in sexual partners.

Children who have been placed in foster care may present with physical sequelae of prior physical or sexual abuse. Physical abuse may result in skin trauma, skeletal fracture, head trauma, abdominal trauma, and chest trauma. Sexual abuse may result in genital trauma or symptoms of STIs. Both can result in mental health needs related to toxic stress and/or complex trauma.

Developmental and Mental Health Issues

A high prevalence of developmental delay, behavioral disorders, and educational difficulties has been noted in foster children of all ages. These disorders are more common in children with a history of neglect or abandonment than in those who have experienced other forms of child maltreatment. Sixty percent of children younger than 5 years entering foster care have significant developmental delays, and 40% of school-age children (age 5 years and older) have school difficulties. Speech and language concerns, delayed fine motor skills, and poor social-adaptive skills are common. Foster children are more likely than their peers who are not in foster care to require special education, experience multiple school placements, and require grade retention. Approximately 30% of children in foster care have behavioral difficulties, and 17% take at least 1 psychotropic or antipsychotic medication, a percentage that is significantly higher than the national average of 5%. Of children taking any psychotropic or antipsychotic drug, a disproportionate number (29%) were children placed in foster care, group homes, or residential treatment centers.

Common mental health issues in the foster care population include attention-deficit/hyperactivity disorder, depression, anxiety, and suicidal ideation resulting from toxic stress. Posttraumatic stress disorder is common and more prevalent in those who have experienced or witnessed family violence. Adolescents in foster care may act out as a manifestation of mental health difficulties, resulting in sexual promiscuity, substance abuse, and truancy, as well as rates of conduct and oppositional defiant disorders that are higher than those in the general adolescent population.

Attachment disorders are more common in the foster care population than in the general pediatric population and account for a portion of the behavioral difficulties in children in foster care. A secure attachment to a primary caregiver is necessary to the development of emotional security and the sense that one's needs are important. Children who are removed from violent homes or who may have experienced abuse or neglect are likely to have never developed a secure attachment to a primary caregiver and therefore may have difficulty bonding with a foster parent. This problem is further compounded if the child is moved between multiple foster homes, prohibiting development of a healthy attachment to a caregiver. In addition to a lack of emotional reciprocity, these children may exhibit self-stimulatory behaviors or sleep disturbances.

The behavioral difficulties manifested in children in the foster care system are often the result of early childhood trauma and toxic stress. Toxic stress changes the neurobiology of the developing brain and can result in emotional dysregulation, impulsivity, and aggression. These children also may be predisposed to behavioral disorders from having been abused or neglected or from having experienced prenatal exposure to drugs or alcohol. Children often experience fear, sadness, and a feeling of guilt or responsibility for the family discord that resulted in their removal. Foster placements are invariably sudden and unexpected, involve the loss of a familiar caregiver, and are traumatic for children of all ages.

Evaluation

It is important for pediatricians to be familiar with the medical consent legalities concerning foster children in their geographic locales. Specifics vary by locality, but generally, foster parents have the authority to provide consent for routine medical care. The placement of a child in foster care does not supersede the right of a biological parent to participate in the medical decision making for his, her, or their child, and many biological parents retain the authority to consent for medical tests and procedures. Any medical procedure or test that requires specific written consent is likely to require authorization by the legally recognized parent (eg, child welfare agency, courts, biological parent). Two common clinical scenarios that frequently require consent beyond the foster parent's authority are HIV testing and the administration of psychotropic medications.

History

Children in foster care may be brought for medical evaluation by an authorized caregiver, who may be a foster parent, a relative of the foster parent, or the social service caseworker. Often the biological parent is absent from the visit and the child's medical records are not available at the time of the evaluation. Obtaining past medical records can be difficult, but the caseworker can be of assistance in this process. It is important to ascertain the circumstances that prompted a child's placement in foster care, because it may be necessary to modify portions of the evaluation accordingly.

Biological family history is useful to evaluate for the presence of genetic disorders and communicable diseases. A maternal history of drug use or STIs is helpful in identifying those children who may have experienced prenatal exposure to drugs or infectious agents.

Birth history should include any history of prenatal care and complications, such as preterm birth or drug withdrawal. Results of routine newborn screening (eg, hearing, inborn errors of metabolism, thyroid function, hemoglobinopathies) should also be obtained.

A complete medical and surgical history should be gathered, including the identification of a regular health professional if the child has one. Older children and adolescents may be able to provide some of their own histories. Known medications and allergies should be documented, and all available immunization records should be obtained. Documentation of a child's immunization history is frequently unavailable; thus, all possible sources of records, such as biological parents or school districts, should be identified. Feeding history and nutritional assessments should include the type and amount of formula or human milk for infants and types and quantities of foods for older children.

The psychosocial history includes a child's current and prior foster placements or living arrangements and whether the child was exposed to domestic violence, physical abuse, or sexual abuse (Box 40.2). Verbal children may also be able to discuss their feelings about their current foster placement. Adolescents should undergo a confidential screening (eg, home, education and employment, activities, drugs, sexuality, and suicide/depression [HEADSS]; see Chapter 4) to address drug, alcohol, and tobacco use; issues related to home and school; sexual activity; violence; and gang involvement.

The developmental history should include the results of prior developmental assessments as well as a listing of therapeutic or early intervention services received. The behavioral history should also include results of prior assessments, mental health services used, and any psychotropic medications prescribed. The foster parent, biological parent, or CPS caseworker may be able to provide useful observations of the child's developmental capabilities, behavioral patterns, and social interactions. The biological parent or CPS caseworker may also be able to assist in collecting records from prior assessments.

Educational history is often not available at the time of the medical evaluation. It is helpful, however, to know a child's history of prior evaluations by the school system, special education services provided, or prior therapeutic services (eg, physical, occupational, or speech therapy) received through the school district.

Box 40.2. What to Ask

Psychosocial Concerns

- When was the child placed in foster care?
- Why was the child placed in foster care?
- Has the child had prior foster placements? If so, when? Why did placement change?
- Was there prior exposure to domestic violence? To physical or sexual abuse?
- Does the child have siblings in foster care?
- How does the child feel about the current foster placement?
- How has the child integrated into the foster family?
- Has the child previously received mental health services or therapeutic services for developmental delay or educational difficulties?
- What is the child's social service plan (eg, parental visits, reunification, termination of parental rights)?
- Does the child have visitation with the biological parents? If so, are visits monitored or unmonitored?
- Do the parents have to participate in any classes or training?

Physical Examination

A complete, unclothed physical examination should be performed on each child. For children who are traumatized or particularly frightened, disrobing only the immediate area being examined may help ease their discomfort. For some traumatized children, more than 1 office visit may be necessary to complete the evaluation. Growth parameters, including height, weight, and occipitofrontal head circumference (for children younger than 2 years) or BMI (for children 2 years and older), should be plotted on a reference chart, and a close inspection should be performed for signs of prior trauma. The child should be assessed for dysmorphic features consistent with prenatal alcohol exposure or other genetic syndromes. In children of all ages, the physical examination should include a genital examination to assess for signs of trauma. Additionally, sexually active females should undergo a pelvic examination if there are any reports of abdominal pain, vaginal discharge, or other concerns. (See Chapters 144–146 for further descriptions of physical findings.)

Immunizations

Immunizations should be administered as appropriate for age, and if immunization records cannot be obtained in a timely fashion (eg, before the next scheduled visit), the child should be considered unimmunized. In this situation, options include restarting the vaccination series or checking antibody titers for selected vaccine antigens (see Chapter 37 for further information). Other possible sources for vaccine records include state or county registry, the child's previous health professional, or the school previously attended by the child. If available, the biological parent should be asked to assist with providing any vaccine record as well as other medical records.

All children should also undergo appropriate screening for tuberculosis, such as purified protein derivative skin testing or interferon-γ release assays.

Additional Assessments

All children should undergo mental health and developmental screenings and should be referred for comprehensive testing if abnormalities are noted. Dental screening should be incorporated in the physical examination of all children older than 6 months. Vision and hearing screenings should also be performed on all children old enough to cooperate. A referral for expert vision or hearing evaluation should be made if it is indicated by the history or physical examination or the patient cannot complete the screening procedure, such as infants and children with developmental delay.

Laboratory Tests

Routine screening laboratory tests should be performed on foster children just as they are indicated for the general pediatric population. For example, hemoglobin level should be checked annually in all infants, toddlers, and preschool-age children. Serum lead

levels should be checked according to local guidelines but should be checked at least once for a child during the toddler years. A urinalysis should be performed as indicated by the history and examination for the child younger than 2 years of age and at least once for the child 2 years of age or older.

For infants younger than 12 months, especially those with a history of prenatal drug exposure or other known risks for maternal STI, rapid plasma reagin, hepatitis C antibody, hepatitis B surface antigen and surface antibody, and HIV testing should be performed.

Adolescents who are considered to have at-risk behaviors, patients with signs or symptoms consistent with an STI, and children with a history of sexual abuse that could result in the transmission of infection should be tested for STIs. Often adolescents can sign their own consent forms for evaluations and treatment related to STIs; however, local statutes should be consulted.

Imaging Studies

If a child has a history or physical findings concerning for physical abuse, imaging such as a radiographic skeletal survey, computed tomography, and magnetic resonance imaging of the head or radionuclide bone scan may be indicated. (For more specific recommendations, see Chapter 17.)

Management

Given the breadth of health-related needs for this patient population and the frequency with which such patients change foster homes, close case management is an essential component of health care delivery to this population. Health professionals should maintain consistent communication with the child's caseworker to ensure that medical and mental health recommendations are incorporated into the child's social service plan. Ideally, a child should have a trauma-informed medical home and continuity with a primary care pediatrician over time. Unfortunately, changes in home placements often make this difficult. If continuity of care is broken, incorporation of the health care plan into a child's broader social service plan should ensure that medical history and medical and mental health recommendations are not lost. The use of electronic health records is a growing practice in many foster care systems and promotes continuity of care, even with logistical challenges.

Children and adolescents in foster care require frequent health visits. The American Academy of Pediatrics recommends a health screening within 72 hours of placement, a comprehensive medical evaluation within 30 days of placement, and a follow-up medical examination within 60 to 90 days after placement. Because of the prevalence of significant medical, social, and mental health issues affecting children in foster care, additional visits are often advisable. Anticipatory guidance should be provided to the caregiver, and age-appropriate issues should be discussed with older children and adolescents.

Children in foster care often need referral to medical subspecialists, dentists, dietitians, speech therapists, occupational therapists, mental health professionals, and other service providers. Case management is necessary to track these referrals and to contact the foster family or caseworker if an appointment is missed.

Prognosis

Children in foster care, spanning in age from newborns to adolescents emancipating from the system, have a spectrum of mental health and medical needs. Preliminary studies have documented improved physical health status, school performance, and adaptive functioning of young children after placement in foster care; however, these studies require replication. The strength of the bond between the foster parent and the child, as well as the consistency and predictability of the foster home environment, are significant to the development of the child's sense of safety and well-being.

To date, much of the research on the health status of children in foster care has focused on the delineation and description of the health-related issues that these children face. More limited evaluation has been done of the different models of health service delivery to the foster care population as well as of the subsequent medical, developmental, and emotional outcomes of the children in these different models.

Although a need exists for continued study of health care delivery to the foster care population, it is widely accepted that children in the foster care system benefit from the establishment of trauma-informed medical homes with case management capabilities and physicians who are well-versed in the complex medical and mental health issues that affect this vulnerable population.

CASE RESOLUTION

This case illustrates many of the common issues that affect children when they are placed in foster care. Medical and immunization records are frequently unavailable to the medical examiner, and chronic medical needs have often gone unmet. This child's poor hygiene and frequent school absences point to a history of parental neglect and, given the presence of drug paraphernalia, her mother likely was involved with substance abuse.

This child should undergo a thorough assessment for behavioral problems, developmental delays, and education-related disabilities. The child states that she does not want to return to her parents' care, but she still misses her family members. This may be remedied through her child welfare plan, for example, by arranging for her to remain in contact with her siblings throughout their foster placement. Because of her experiences in her prior home environment, she has depressive symptoms and is likely to have other unmet mental health needs, which require referral to a mental health provider. She also needs evaluation by her new school system to determine her specific educational needs and appropriate grade placement.

The girl has poor dentition, which is a common finding in the foster care population, and she requires a referral for dental care. The presence of mild wheezing in a child who states that she feels fine otherwise is a likely marker for untreated reactive airway disease and may be a reflection of poor continuity of medical care prior to her placement. Routine adolescent care should be initiated at this visit, including a thorough history of drug and alcohol use as well as reproductive history. Anticipatory guidance on menstruation, sexuality, and drug use should be considered. Her vaccines should be updated. She should be scheduled for a revisit in 2 months for the second human papillomavirus vaccine and to establish an ongoing relationship, monitor her asthma, and talk about any concerns she may have.

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CHAPTER 41

Working With Immigrant Children and Their Families

Ismael Corral, MD, MBA, and Carol D. Berkowitz, MD, FAAP

CASE STUDY

A 7-year-old boy presents with vomiting and clinical signs of dehydration. The family thinks he has empacho (a Latin American folk illness). You tell the family that you suspect that he has viral gastroenteritis. You want to draw some blood samples for testing and give him fluids intravenously. The parents are skeptical; they refuse the blood work and want to leave, against medical advice.

Questions

1. What are the ways in which different immigrant families view illness and health?
2. What are barriers to accessing health care that children in immigrant families face?
3. What questions help the physician understand the health beliefs of immigrant families?
4. What are the considerations when interacting with parents who do not speak English?

The United States is described as a nation of immigrants. Out of a population of 326 million, current estimates are that about 43 million, or approximately 13.2% of the current US population, are foreign-born citizens or noncitizens. Half of these immigrants are Hispanic, and 65% of Hispanics are of Mexican descent. It is expected that by 2030, Hispanic children will account for most children living in the United States. During the 1990s, 70% of the overall US population growth was influenced by a wave of recent immigrants, mostly from Latin America and Asia, and by the children born to these newcomers. The vast growth in the population of children living in immigrant families, whether foreign born (first generation) or US born (second generation), poses a unique set of challenges. This is especially the case in 10 major metropolitan areas that are classified as traditional immigrant destinations, where approximately 48% of immigrant children reside. While this chapter focuses on immigrant children, children of migrant workers, and children living by the United States-Mexico border may face similar issues related to access to quality health care.

Households with immigrant children are more likely to live below the federal poverty level (FPL) and have at least 1 parent who did not graduate high school or is not fluent in English. An estimated 31% of mothers and a similar number of fathers in these families have not graduated from high school. In 2013, 26% of children in immigrant families lived below the FPL, compared with 19% of children whose parents were born in the United States. This has gradually increased since 2006, when 22% of children in immigrant families lived below the FPL. These children are also more likely to live in crowded housing (>1 person per room) and in a multigenerational household. Families of immigrant children tend to be larger, with 19% having 5 or more children, compared with families of children born in the United States, of which only 14% are of that size. While some immigrant children are citizens and eligible for safety net programs, their family's status directly influences whether these children will even access such care. Children of immigrant parents are twice as likely to be uninsured (15%) as children in nonimmigrant families (8%). There is also growing concern that the health status of some immigrant children, whether foreign born or first generation, actually declines after settling in the United States.

Demographics of Immigrant Children

There are 5 general categories of immigrants in the United States, each benefiting from specific entitlements and services and having certain legal rights: lawful permanent residents, naturalized citizens, refugees/asylees, nonimmigrants, and undocumented immigrants (Box 41.1).

In 2007, individuals who had become naturalized citizens included immigrants (32%), lawful permanent residents (29%), undocumented immigrants (29%), refugees (7%), and nonimmigrants (3%). From 1980 to 2000, the children of immigrants increased from 5% to 20% of school-age children, representing approximately 10 million of the estimated 60 million school-age children in the United States.

By far the largest category of immigrants is nonimmigrants or temporary visitors. Approximately 3 million children arrive each year, mostly from Asia, Western Europe, and parts of North America, typically accompanying their parents, who are seeking

Box 41.1. Categories of Immigrants in the United States

Lawful Permanent Residents

- Carry a green card.
- Noncitizens with permission to permanently live and work in the United States.
- May apply for naturalization after 5 years (or 3 years if they marry a citizen).
- Group with the most international adoptees.

Naturalized Citizens

- Born as noncitizens.
- Having met certain English literacy requirements and demonstrating a basic knowledge of civics and a desirable moral character, are granted the same rights as natural-born citizens.
- However, are not eligible to hold the office of president or vice president.

Refugees/Asylees

- Granted permission from the US government before entry.
- Fled their country of origin for fear of persecution because of their race, religion, social group, or political opinion.
- Many unable or unwilling to return to their country of origin.
- Those granted permission to remain are deemed *asylees*.
- After a year, both may apply to adjust their status to lawful permanent resident.

Nonimmigrants

- Carry a visa.
- Granted permission to enter for a specified time and specific purpose (usually to work or study).

Undocumented Immigrants

- Entered the country illegally or even legally but then violated the terms of their stay and remained after their visa expired.
- Lack proper papers and identification to live in the United States.

work. A smaller percentage are students or exchange visitors. While not technically immigrants, this special group may present for care with similarly unaddressed health issues depending on their country of origin.

The next largest group, almost a quarter-million children, enter the United States as lawful permanent residents, with most eventually becoming naturalized citizens. Although most arrive with or to meet family already residing in the United States, several thousand adolescents immigrate unaccompanied each year; most are female, and many are married to a naturalized citizen at the time of immigration. Included in this group are children of refugees or asylees. More than 75,000 individuals arrive each year, most recently from the countries of the former Yugoslavia and former Soviet Union, Vietnam, Somalia, and other war-torn regions. Numbers for the third-largest group, undocumented immigrants, are based primarily on estimates. Most are from Mexico or other Latin American states. Some entered the United States legally but have overstayed their visa or lost their status by committing a crime.

While most pediatricians are not in a position to assist families in their efforts to attain citizenship or legal status, programs such as the National Center for Medical-Legal Partnership (https://medical-legalpartnership.org) may provide necessary advice and services. There is also an Immigrant Child Health Toolkit available through the American Academy of Pediatrics (AAP) that provides primary care physicians with immigration-specific resources readily available within their area.

Health Care Needs of Immigrant Children

When the child of an immigrant family presents for care, primary concerns are about the presence of an infectious disease (from exposures and possible lack of vaccination) or of a hidden genetic or ethnic condition (eg, hemoglobinopathies, glucose-6-phosphate dehydrogenase deficiency). Investigating the health status of a child, especially from undocumented immigrant families, is paramount because these children likely have not seen a doctor prior to immigrating. Similarly, nonimmigrants, such as tourists and other temporary visitors, from many Western or Pacific Rim countries are not required to have a medical examination performed as part of their application. Only visas for permanent residency require a health examination to be performed by an approved physician, and even then, the focus of the examination is to exclude certain conditions, such as active tuberculosis (TB), HIV, and other severe physical or mental disabilities. In children, laboratory testing may be limited, and proof of vaccination status may be exempted for certain groups, such as international adoptees.

Lack of education and poverty, which results in relative food insecurity and inadequate, crowded housing conditions, poses an ominous threat to the health of these same children. Immigrant parents of children born in the United States may be reluctant to apply for Medicaid or the Children's Health Insurance Program for fear of being considered a public charge (ie, a person dependent on the government for expenses of living). The Patient Protection and Affordable Care Act of 2010 excluded undocumented immigrants from health care coverage. Noncitizen children who are lawful permanent residents must wait at least 5 years before they are able to apply for public assistance. While most refugee children may receive some form of subsidized care, such as Medicaid, many of these benefits are time-sensitive. Even US-born children of undocumented mothers, while legally eligible as US citizens for benefits such as nutritional assistance programs, may not receive these because of parental fears of detection and deportation.

Physicians should ascertain that the family has adequate housing and access to food, 2 basic human needs. The physician should take the following factors into consideration during health supervision visits (Box 41.2): Is the food available in the family's neighborhood consistent with the traditional food that the family desires? Is the food healthy, or does the family live in a food desert where there is a plethora of fast-food restaurants and a paucity of supermarkets or grocery stores? The ability to safely attend the local park, walk around the neighborhood, or even go outside the family's own

Box 41.2. Risk Factors Affecting the Health of Immigrant Children

Social and Economic
- Inadequate or crowded housing
- Environmental safety concerns
- Food insecurity
- Lack of insurance (because of ineligibility)
- Lack of access to insurance (eligible but unable or unwilling to apply)
- Educational level of household

Cultural
- Dietary preferences
- Lack of language fluency or literacy and translation/interpretation issues
- Disparate ideas about the causation and treatment of illness
- Expectations of the medical system
- Religious practices with a medical component
- Lack of access to traditional medical practitioners and treatments
- Importation of drugs not approved in the United States

Physical
- Carriage of infectious disease and the possibility for repeated exposure via travel or living within one's immigrant community
- Presence of ethnic or genetic variations
- Lack of vaccination
- Poor nutritional status

Mental Health
- Negative past living conditions, including exposure to violence or natural disaster
- Cultural adjustment (or the process of acculturation or enculturation)
- Traumatic separation

home should be determined, as any of these factors may interfere with treatment plans. In cases in which safety or access is an issue, information about local community centers should be provided during clinic visits. Often, families may not be aware of affordable, local, easily accessible resources.

It has traditionally been supposed that immigration itself imposes unique stresses on these children. Mental health challenges (eg, depression, anxiety, grief) may be related to the reasons for their migration as well as to the inevitable process of acculturation. Stress is compounded by the potential loss of the immigrant's identity, separation from home support systems, or traumatic separation from family members either in the United States or during travel; inadequate language and literacy skills in a society intolerant of linguistic weakness; disparities between one's country of origin and the United States in economic, social, and professional standards and status; and the psychological and emotional trauma of war, persecution, or exploitation in one's country of origin.

Despite these challenges, epidemiological studies indicate that children in immigrant families experience better outcomes than those in their native countries who did not immigrate, especially in some countries. The most striking example is the lower rate of low-birth-weight children born to foreign-born mothers, especially among Hispanic and non-Hispanic black immigrants, compared with women in their native countries who did not immigrate. This positive effect related to immigration has been studied less in older children because of limited availability of data samples from second-generation children that do not exclude first-generation children.

General Approach to the Initial Medical Evaluation of an Immigrant Child

Ascertaining the life history of an immigrant child, including any relevant travel history, will help determine the extent of the medical evaluation (Box 41.3).

In general, most immigrants from industrialized nations have received comprehensive medical care, and the only issues facing these children are routine, such as updating immunization status. In contrast, adoptees, refugees, and undocumented children often have received little or no care. While there is no single approach to the medical evaluation of all immigrant children, some general principles apply.

Any and all existing medical records should be reviewed. Previous growth parameters should be obtained, if available. While a complete translation is not always necessary, if an unusual diagnosis or a complicated history exists, use of clinical translational services or a nearby university's academic language department may facilitate the process. Sometimes, records suggest that a diagnosis was considered but not confirmed, and it may be appropriate to reevaluate the child for any suspected condition.

It is important to screen for certain infectious diseases. The most common among immigrants are TB, intestinal parasites, hepatitis B, syphilis, and HIV. In fact, the risk of TB is more than 100 times greater in immigrant children than in US children. Fifty percent of all newly identified cases of TB in the United States are diagnosed in immigrants, many within the first 5 years after birth. If TB is not clinically apparent (ie, in the incubation period), or test

Box 41.3. What to Ask

Evaluating Immigrant Children
- Are the parents present? Or is there a current guardian who may have personal knowledge of the child's social and medical history?
- In which countries has the child resided and under what circumstances?
- Have the child's living conditions changed dramatically (positively or negatively) recently?
- Are there verifiable birth and medical records to be reviewed? Vaccination status? What age is the child? What type of health care did the child receive in his or her home country?
- Has the child undergone any recent procedures or treatment?
- Was the child exposed to any potentially toxic occupational or environmental risks?
- What educational level did the child achieve?

results are negative but clinical suspicion exists, TB testing should be repeated in 6 months. The AAP *Red Book* can provide guidance on interpreting tuberculin skin tests in the setting of BCG vaccine as well as advice about alternative tests, if warranted. Intestinal parasitic infestations may be present without symptoms. Some clinics specializing in immigrant health advocate giving a single dose of albendazole as a more cost-effective approach than screening and diagnosis, but the safety and efficacy of this approach has not been substantiated in children.

Ethnic or genetic conditions should also be considered. Conditions such as glucose-6-phosphate dehydrogenase deficiency in immigrants from the Mediterranean, Africa, and Southeast Asia may affect the child's health in the short term. Others, such as hemoglobinopathies and thalassemia, while common among certain ethnic populations, such as those from Southeast Asia, may not be of immediate importance. Overall, anemia is extremely common among immigrant children, and the diagnostic workup of these children may uncover an underlying blood dyscrasia trait or lead intoxication. If iron therapy has been initiated empirically, repeat testing after treatment is paramount to ensure a response and confirm the diagnosis. Understanding the risk of nutritional deficiencies based on the country of origin is important. For instance, nutritional disorders, such as rickets and iodine deficiency, are common in children who are ethnic Chinese and children from the former Soviet Union.

Immunizations must be administered as appropriate, following the catch-up recommendations of the AAP and the Advisory Committee on Immunization Practices. Records of previous immunizations may be difficult to interpret. Shortened intervals or the administration of a vaccination at too early an age may not be readily apparent. Fraudulent records, especially among adoptees and children from institutional settings, often exist. In young children, it is generally considered safe and cost-effective to simply give missing vaccines; however, determining serum immunity through the use of titers may be more cost-effective in older children. It is also important to remember that children seeking asylum are not required to meet immunization requirements at time of entry; however, at time of permanent residency application they must show proof of immunization.

Cultural and Linguistic Sensitivity

Bridging language differences using professional interpreter services is required to provide adequate patient care. Such linguistic services are mandated by agencies such as the Centers for Medicare & Medicaid Services for payment from the federal government. The use of children or hospital maintenance or janitorial staff as interpreters is inadequate and potentially violates federal laws, including the Health Insurance Portability and Accountability Act of 1996. Professional interpreters are taught to interpret and not carry on additional conversations with the patient or expound on the questions the physician asks. The physician should address questions directly to and maintain eye contact with the patient, not the interpreter.

Communicating in a patient's native language serves to foster and enhance the physician-patient relationship. Patients often feel more relaxed, confident, and open to sharing their concerns with their physician. Treatment plans expand beyond a physician-directed plan to a dynamic interaction that empowers the patient to take control of the disease.

Providing culturally competent care that considers cultural practices and beliefs about child health or illness when devising a treatment plan is also critical. Questions to ask are provided in Box 41.4 and also include the following: Does the family access healers for medical problems? What are the family's views about medication use? Are there hierarchical structures that influence a parent's acceptance of a physician's advice (eg, father accepting advice from a female physician, parent accepting advice from a young resident)? Are there dietary restrictions? In addition, it is important to consider the influence of socioeconomic status and environmental hazards during the development and implementation of a treatment plan. Failure to take all these factors into account may lead to undesired health outcomes and incorrectly labeling the family or patient as noncompliant.

Conclusion

There are numerous barriers that potentially interfere with achieving optimal health status for immigrant children. Many of these barriers are societal and relate to funding for medical services. Trust is a core component of the physician-patient relationship, and establishing trust may be more difficult when the physician and family have different cultural values and expectations. It has been stated that in medicine, the sacred trust that develops between a patient and his or her doctor should never be taken for granted. The development of trust forms the foundation of the therapeutic relationship. It provides credibility to the practitioner. The practitioner must act in a manner that elicits and fosters trust, and being knowledgeable and nonjudgmental about the beliefs and practices of patients is pivotal.

Box 41.4. What to Ask

Understanding Cultural Concepts of the Symptoms of Illness

- What do you call the problem? What is your understanding of the problem?
- What do you think caused it?
- Why do you think it started when it did?
- What do you think the sickness does? How does it work?
- How severe is it? How long will it last?
- What are the chief problems the illness has caused?
- What kind of treatment do you think the child should receive? What are the most important results you expect from this treatment?
- What do you fear most about the illness? Do you fear the treatment or medication?

Adapted from Kleinman A. *Patients and Healers in the Context of Culture: An Exploration of the Borderland Between Anthropology, Medicine, and Psychiatry*. Berkeley, CA: University of California Press; 1981.

Health professionals must work toward creating an atmosphere of trust so that parents feel comfortable revealing their beliefs, concerns, and fears. The threat of deportation should be considered when taking into account whether the patient or family will follow up or adhere to medical recommendations.

It is unwise not to acknowledge the cultural divide that exists between most pediatric practitioners and the families they serve. Therefore, pediatricians who are less familiar with the enrichment provided by a multicultural patient population may be less inclined to advocate for social reforms that may prove beneficial. Physicians must approach families with an open mind, respect, and a sense of humility if they are to gain families' trust, close the gaps that separate, and promote the well-being of children.

Children are better served when their families receive information about federal, state, and community programs that provide resources to immigrant families. In addition to health care, pediatricians can provide families with information about educational programs, such as Head Start, that are not restricted by immigration status. All children, regardless of their immigration or socioeconomic status, should receive compassionate, culturally competent, and linguistically effective care services. Such care requires that health professionals incorporate knowledge, attitudes, and skills in cultural and linguistic competence within their professional agenda.

The well-being of all children can be advanced through advocacy, especially on behalf of vulnerable children. Such advocacy addresses outreach efforts to children who are potentially eligible for Medicaid and the Children's Health Insurance Program but are not enrolled, simplifies enrollment for both programs, and expands state funding for those who are not eligible. The medical community must collaborate with legislators, families, and organizations representing underserved populations to increase the effectiveness of one's own advocacy effort. All children should receive care in a medical home (ie, the establishment of comprehensive, coordinated, and continuous health care services). This is especially critical for immigrant children with chronic and mental health care needs.

CASE RESOLUTION

You reach an agreement with the family for a community healer to come and perform a therapeutic massage while allowing you to place an intravenous line and administer fluids. The patient is significantly improved after the massage and intravenous fluids. The family appreciates that you respected their beliefs and agrees to return for a routine health supervision visit in 2 weeks.

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CHAPTER 42

Well-Child Care for Children With Trisomy 21 (Down Syndrome)

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CASE STUDY

A 6-month-old girl with trisomy 21 (ie, Down syndrome) whom you have known since birth is brought to your office for well-child care. She and her parents have been doing well, although she has had several episodes of upper respiratory infections. Her medical history is significant for a small ventricular septal defect, which has since closed spontaneously, as well as 1 episode of otitis media at 5 months of age. Her weight gain has been good—along the 25th percentile on the growth chart for children with Down syndrome. Currently, she sleeps through the night and has a bowel movement once a day. She has received all the recommended immunizations for her age without any problems.

The infant smiles appropriately, grasps and shakes hand toys, and has some head control but cannot roll from supine to prone position. Since 1 month of age, she has been enrolled in an early intervention program. An occupational therapist visits her at home twice a month.

On physical examination, she has typical facial features consistent with trisomy 21, a single palmar crease on each hand, and mild generalized hypotonia. Her eyes have symmetric movement, and her tympanic membranes are clear. She has no cardiac murmurs.

Questions

1. What is the prevalence of trisomy 21 (ie, Down syndrome) in the general population? What is the association of maternal age with trisomy 21?
2. What are the clinical manifestations of Down syndrome?
3. What medical conditions are associated with trisomy 21 in the newborn period, during childhood, and in adolescence? When should screening tests for these conditions be performed?
4. What is the role of early intervention services for patients with trisomy 21 and their families?
5. What specific psychosocial issues should be included in the anticipatory guidance and health education provided by the physician?
6. What is the prognosis for the child with trisomy 21?

Trisomy 21, or Down syndrome, is the most common genetic cause of intellectual disability in children. Primary care physicians are in a unique position to offer affected children specific health maintenance and anticipatory guidance, help manage intercurrent illness and chronic problems, and apply the latest recommendations for clinical screening based on risks for conditions associated with trisomy 21. Additionally, the general pediatrician has the opportunity to develop rapport with children and families, which is of particular importance because of the complex medical and social implications of raising a child with trisomy 21. An important goal of the well-child visit is to provide children with trisomy 21 and their families with counseling about educational, social, and financial resources and support to ensure a healthy and productive transition into adulthood.

Epidemiology

According to the Centers for Disease Control and Prevention, the prevalence of trisomy 21 is approximately 1 in 700 live births in the United States. It is estimated that trisomy 21 is responsible for up to one-third of all cases of moderate to severe intellectual disability. Trisomy 21 has a male-to-female ratio of 1.3:1.

Ninety-five percent of all cases of Down syndrome are caused by chromosomal nondisjunction, and most of these events occur in oocytes during meiosis. The probability of maternal chromosomal nondisjunction is determined by maternal age. A 25-year-old woman has a 1 in 1,240 risk for having a live baby with Down syndrome, and the risk increases to 1 in 340 at age 35 years and 1 in 98 at age 40 years. It is estimated that approximately one-half of

trisomy 21 embryos abort spontaneously. The risk of recurrence of the nondisjunction type of Down syndrome in subsequent pregnancies is 1 in 100 until age 35 years, after which the risk determined by age takes precedence. Other family members generally are not at increased risk of bearing children with this type of Down syndrome.

Recent advances in first and second trimester screening allow prenatal diagnosis of Down syndrome with a sensitivity of 80% to 90%. If a prenatal diagnosis of Down syndrome is made and the general pediatrician is asked to participate in counseling the family, the pediatrician should go over with the family the points listed in Box 42.1.

Clinical Presentation

Newborns, infants, and children with trisomy 21 have a characteristic appearance (Box 42.2). They may exhibit microcephaly, with flattening of the occiput and face. The eyes have an upward slant with prominent epicanthal folds, the ears are small and set low, the nasal bridge is flattened, and the tongue appears large. The feet, hands, and digits are small and stubby (ie, brachydactyly), and the fifth digit may be hypoplastic and turned in (ie, clinodactyly). A single palmar crease and wide spacing between the first and second toes may be evident. After the newborn period, diffuse hypotonia and developmental delay are universally seen.

Box 42.1. Counseling the Family After a Prenatal Diagnosis of Down Syndrome

- Review the data that established the diagnosis in the fetus.
- Explain the mechanism of occurrence and risks for recurrence.
- Review the manifestations of trisomy 21, commonly associated conditions, and the variable prognosis based on the presence of these conditions.
- Discuss other modalities that confirm the presence of associated anomalies, such as fetal echocardiography in the case of congenital heart disease.
- Explore treatment options and interventions for associated conditions.
- Offer resources to assist the family with decisions about completing or terminating the pregnancy.
- Refer the family to a clinical geneticist or genetic counselor.

Box 42.2. Diagnosis of Trisomy 21

- Microcephaly, with flattening of occiput and face
- Upward slant to the eyes with epicanthal folds
- Brushfield spots on the irises
- Small ears and mouth (tongue appears large in relation to the mouth)
- Low-set ears
- Flat nasal bridge
- Broad, stocky neck with loose skin folds at the nape
- Funnel-shaped or pigeon-breasted chest
- Small, stubby feet, hands, and digits (ie, brachydactyly); the fifth digit may be hypoplastic and turned in (ie, clinodactyly)
- Single transverse palmar crease on each hand
- Wide space between first and second toes
- Fair, mottled skin in newborns; dry skin in older children
- Hypotonia

Pathophysiology

Down syndrome is caused by trisomy 21 resulting from meiotic nondisjunction (approximately 95% of cases), translocation (3%–4% of cases), and mosaicism (1%–2% of cases). A small percentage of affected children have a chromosomal rearrangement resulting in 3 copies of a portion of chromosome 21.

Translocations in an affected child are unbalanced and usually occur between chromosome 21 and another acrocentric chromosome, most commonly chromosome 14 or 15. Approximately 75% of these translocations are de novo rearrangements, and 25% are the result of a familial translocation. In the latter case, a parent may be an unaffected carrier of a balanced translocation involving the long arms of chromosome 21 and another acrocentric chromosome (ie, robertsonian translocation). Thus, if a child is found to have a translocation, parental karyotypes must be assessed because balanced translocation carriers have an increased risk of Down syndrome in future children. Mosaicism implies the presence of 2 cell lines—1 normal and 1 with trisomy 21. As might be expected, children with mosaic Down syndrome are usually affected less severely than children with other types of Down syndrome.

Research has focused on the role of individual genes, such as *DYRK1A*, in the pathogenesis of Down syndrome. It is expected that in the near future, pharmacologic agents that mitigate the effects of excess expression of such genes will result in new treatments for patients with Down syndrome.

Evaluation

Routine health maintenance for newborns, infants, children, and adolescents with trisomy 21 should include discussion of the same issues of health education, prevention, and counseling that are discussed with other patients and their families. The schedule of health maintenance visits for newborns, infants, and young children with trisomy 21 is essentially the same as that recommended by the American Academy of Pediatrics for other children, whereas older children with Down syndrome should be evaluated annually. Surveillance and anticipatory guidance related to the additional medical and psychosocial conditions common among patients with trisomy 21 is tailored to the main periods in a child's life: newborn, infancy and early childhood, and older childhood and adolescence.

Newborn Period

Verification of the diagnosis of trisomy 21 is perhaps the single most important focus of the initial family visit. Sometimes the diagnosis has been suspected prenatally because of abnormal biochemical markers and sonographic findings and verified by chorionic villus sampling or amniocentesis (Box 42.1). If no prenatal testing data are available and the diagnosis is suspected based on clinical findings,

a karyotype test must be performed while in the nursery and the results reviewed at the 1- to 2-week visit. In some institutions, a fluorescence in situ hybridization test for trisomy 21 may provide a more rapid confirmation of the diagnosis (1–3 days).

Several conditions associated with trisomy 21 are important to identify in the newborn period, including hearing loss, congenital heart disease (most commonly endocardial cushion defect), duodenal atresia, Hirschsprung disease, congenital hypothyroidism, hip dislocation, and ocular anomalies (ie, cataracts, glaucoma, strabismus, nystagmus). Hematologic abnormalities include polycythemia, leukemoid reactions that resemble leukemia but resolve during the first month after birth, and, rarely, leukemia.

History

A feeding history is critical because hypotonia often results in difficulty swallowing (Table 42.1). A history of vomiting may be indicative of gastroesophageal reflux or, less commonly, gastrointestinal malformation. Constipation may be the first indication of Hirschsprung disease or hypothyroidism. A detailed family and social history should also be obtained if this was not done in the hospital.

Physical Examination

A detailed physical examination should reveal some common features of newborns with Down syndrome (Box 42.2). All growth parameters should be recorded and compared with those obtained at birth. The size of the fontanels should be evaluated because of the increased incidence of congenital hypothyroidism in this population. Bilateral red reflexes and conjugate gaze should be documented to exclude congenital cataracts or strabismus. A careful cardiac examination must be performed, noting any cyanosis, murmurs, irregular heart rates, abnormal heart sounds, or asymmetry of pulses. The abdomen should be palpated for organomegaly or any masses, and patency of the anus should be verified. Ortolani and Barlow maneuvers should be performed for hip laxity. Finally, the newborn should be evaluated for hypotonia.

Laboratory Tests

Karyotyping is an important tool in verifying the diagnosis and assessing the risk of recurrence. Newborn screening laboratory tests must be reviewed, especially hearing evaluations and thyroid screenings. Additionally, a cardiac evaluation for congenital heart disease should be performed, which may include electrocardiography, chest radiography, echocardiography, and formal cardiology referral. A complete blood cell count is indicated to assess for hematologic abnormalities, including leukemoid reaction, transient myeloproliferative disorder (ie, pancytopenia, hepatosplenomegaly, and immature white blood cells), and neonatal thrombocytopenia.

Management

The primary care physician should discuss the increased propensity for respiratory infections in children with Down syndrome. Other important issues to address include those pertaining to available resources for children and families, such as early intervention programs and Down syndrome support groups in the community.

Table 42.1. Health Supervision for Children With Down Syndrome

Evaluation Type	*Assessment*	*Age at Initial Evaluation*	*Timing of Subsequent Evaluations*
History and physical examination	Developmental Visual and hearing (subjective)	Newborn	Same as regular well-child care schedule until age 5 years, then annually.
Laboratory assessment	Karyotyping	Newborn	None.
	Thyroid screening	Newborn screening	6 months and 12 months, then annually thereafter.
	Complete blood cell count	Newborn	0–1 month, after which hemoglobin level is assessed annually.
	Celiac screening	2–3 years	Measure tissue transglutaminase IgA antibody levels.[a]
	Echocardiography	Newborn	Condition dependent.
	Neck radiography	3–5 years	Obtain in symptomatic individuals with pain or neurologic abnormalities. May be required for Special Olympics entry.[b]
Consultation	Genetics	Newborn	As needed.[c]
	Cardiology	Newborn	Condition dependent.
	Ophthalmology	6 months	Annually until age 5 years, then every 2 years until age 13 years, then every 3 years.
	Ear, nose, and throat	As needed	As needed.
	Dental	By 1 year	Twice per year.
	Pulmonary	As needed	As needed.

[a] Lack of expert consensus on evaluation. Some recommend testing every 5 years and others recommend testing only symptomatic individuals.

[b] Lack of expert consensus on evaluation.

[c] Depending on experience and comfort level of primary care physician.

Educational materials, such as pamphlets and books, may also be supplied at this time. Upcoming appointments with other physicians and allied health professionals should be reviewed.

Infancy and Early Childhood

History

Some additional history-related issues to address include a detailed developmental assessment focusing on progress made since the previous visit, because most affected children have motor and speech delays (see Table 42.1). It is important to review any ancillary services, such as physical, occupational, and speech therapy, in anticipation of school entry. The parent or parents should provide their assessment of the child's vision and hearing. A history of recurrent respiratory infections is concerning for recurrent otitis media with the associated risk of hearing loss. Many children with trisomy 21 experience constipation. A history of snoring and restless sleep may be indicative of obstructive sleep apnea, and a sleep study may be necessary. Finally, it is extremely important to document any history of neck pain, gait changes, increased clumsiness, or other neurologic symptoms that would be indicative of spinal cord compression resulting from atlantoaxial dislocation.

Physical Examination

All growth parameters should be plotted on growth charts specific to children with Down syndrome (Figures 42.1 and 42.2). Children with trisomy 21 are shorter than other children and may have poor weight gain in their first year. Later in life, obesity unrelated to the syndrome may become a problem. As with routine well-child visits in other infants and children, a complete physical examination should be performed at each patient encounter. Noteworthy aspects of the examination in infants and children with trisomy 21 are presented in Box 42.3. In particular, the ear canals of these children are easily collapsed, making it difficult to visualize the tympanic membrane. In some cases, referral to an otolaryngologist may be necessary for an adequate otoscopic examination. A complete neurologic examination should be performed at each visit, including an assessment of the severity of hypotonia.

Laboratory Tests

Hearing evaluation should be performed annually, starting with the newborn hearing screening. Developmentally appropriate gross visual screening should be performed at each visit in infants between 6 and 12 months of age, and a formal ophthalmologic examination is recommended starting at 6 months of age. Thyroid screening tests should be repeated at 6 and 12 months and then annually.

Children with congenital heart disease should be given antibiotic endocarditis prophylaxis for dental or other procedures. Additionally, these children should be considered for monoclonal antibody therapy against respiratory syncytial virus in the winter.

Children with Down syndrome are at increased risk for autoimmune disorders, such as celiac disease, Graves disease, and type 1 diabetes. Because the signs of celiac disease may be subtle, some pediatric gastroenterologists recommend measuring tissue transglutaminase immunoglobulin A antibodies as well as an immunoglobulin A level, at 2 to 3 years of age and every 5 years thereafter. Current American Academy of Pediatrics recommendations include screening only symptomatic children, however.

Children with Down syndrome have an increased incidence of atlantoaxial instability when screened with routine lateral cervical radiographs with flexion and extension views. Any patient with signs or symptoms of spinal cord compression should be evaluated on computed tomography or magnetic resonance imaging and referred to an orthopedic surgeon or neurosurgeon. The symptomatic child should be kept out of any sports that involve contact or neck extension, such as swimming, gymnastics, and soccer. Experts agree that careful neurologic screening at health supervision visits is a much better predictor of serious injury than cervical radiographs. The current recommendation is to screen only symptomatic children, unless a preparticipation radiograph is required for events, such as the Special Olympics.

Management

Infants with trisomy 21 should undergo all routine screening tests and immunizations. Growth and developmental progress should be reviewed with the parent or parents at the end of each visit, and any concerns or unmet expectations should be addressed at this time. Often the developmental delay associated with trisomy 21 is not apparent to families until an infant is 4 to 6 months of age and not achieving the expected milestones of rolling over or sitting. It should also be emphasized to families that the severity of intellectual disability in trisomy 21 is quite variable, ranging from mild to severe. Social function is not necessarily related to IQ, however. If the child is not already enrolled in an early intervention program, the physician should emphasize to the parent or parents the positive role of such an experience. The availability of support groups for parents and other family members should also be discussed. The role of support groups may be especially beneficial to the patient with both Down syndrome and autism spectrum disorder.

In the early childhood years, plans for preschool attendance and future educational opportunities should be reviewed with the family. The role of discipline and the presence of common behavioral problems, such as temper tantrums and biting, should be assessed in preparation for school entry and socialization. Nutrition should be reviewed, because children with Down syndrome have a reduced basal energy expenditure and are at increased risk for obesity. Nutritional supplements and other alternative medicines have not been proved to have any efficacy in the treatment of patients with Down syndrome.

As is recommended for all children, a dental referral should be made by 1 year of age.

Older Childhood and Adolescence

History

School-age children with Down syndrome should continue to visit their primary care physician at least annually. Educational issues should be discussed, including the Individualized Education Program and transition from school. Specific medical issues to

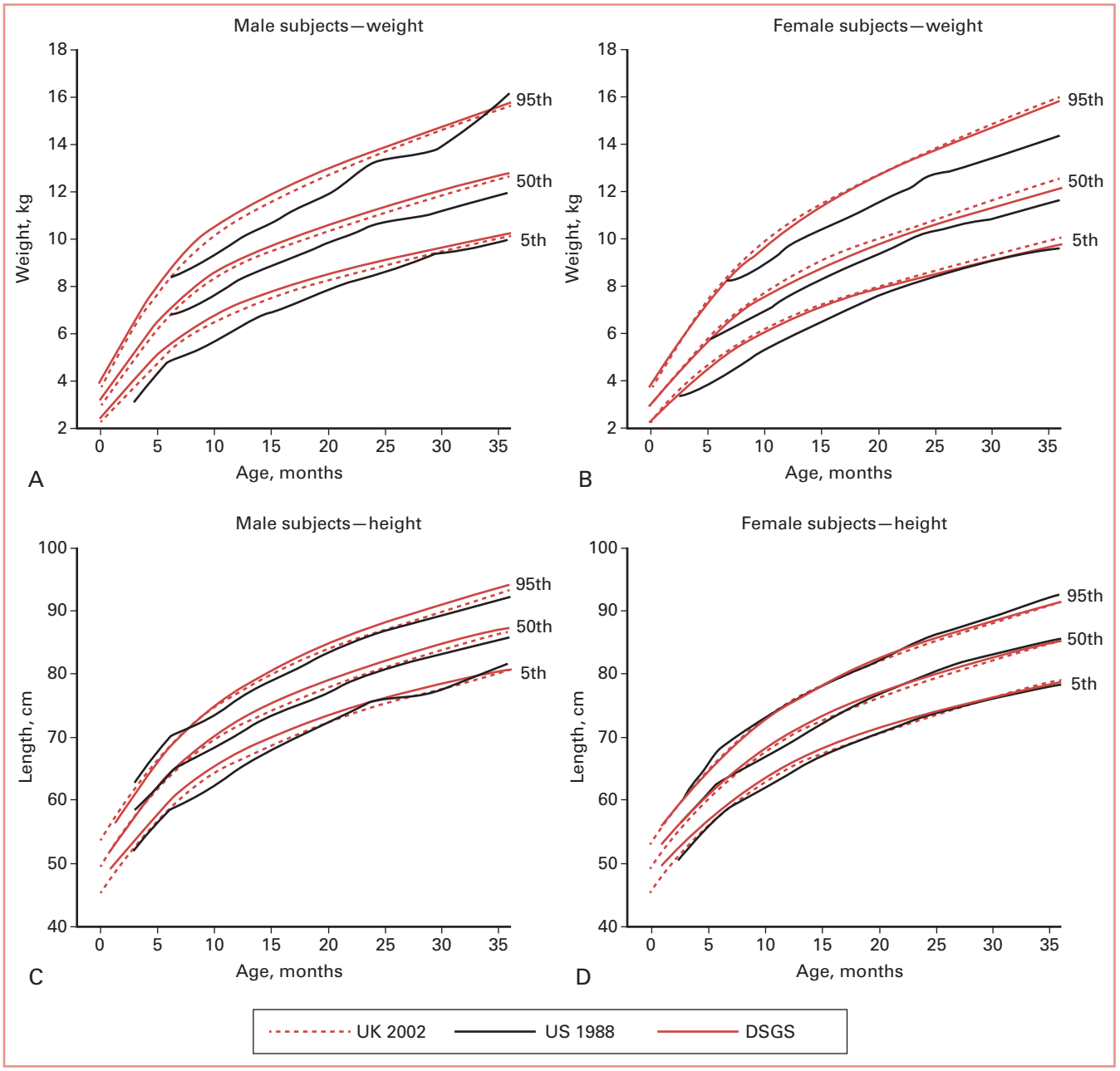

Figure 42.1. Curve comparisons for weight in kilograms and length in centimeters for male and female subjects, birth to 36 months of age. Contemporary curves from the Down Syndrome Growing Up Study (DSGS [solid line]) are compared with those from the US 1988 curves from Cronk et al (dotted line) and the UK 2002 curves from Styles et al (dashed line).

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address during the history include visual or hearing deficits; evidence of hypothyroidism (ie, decreased activity, coarse and dry hair, constipation); skin problems, including eczema; and dental problems. A careful nutritional history should also be obtained because of the propensity for obesity, and the child should be closely monitored for signs of obstructive sleep apnea.

Physical Examination

The physician should continue to plot height and weight measurements. The skin should be examined closely for xerosis, acne, or syringomas (ie, multiple papules, often present on the eyelids and upper cheeks) during adolescence. A cardiac examination is important because of an increased risk of mitral valve prolapse and valvular dysfunction. The sexual maturity rating (ie, Tanner stage) of all patients should be noted and discussed with the parent or parents. A pelvic examination is not indicated as a part of the routine visit unless concern exists for sexual abuse or a sexually transmitted infection; however, a testicular examination is important because of the increased risk for testicular cancer in patients with Down syndrome. Patients who participate in sports and other physical activities should undergo a complete neurologic examination to assess for signs of impending atlantoaxial dislocation.

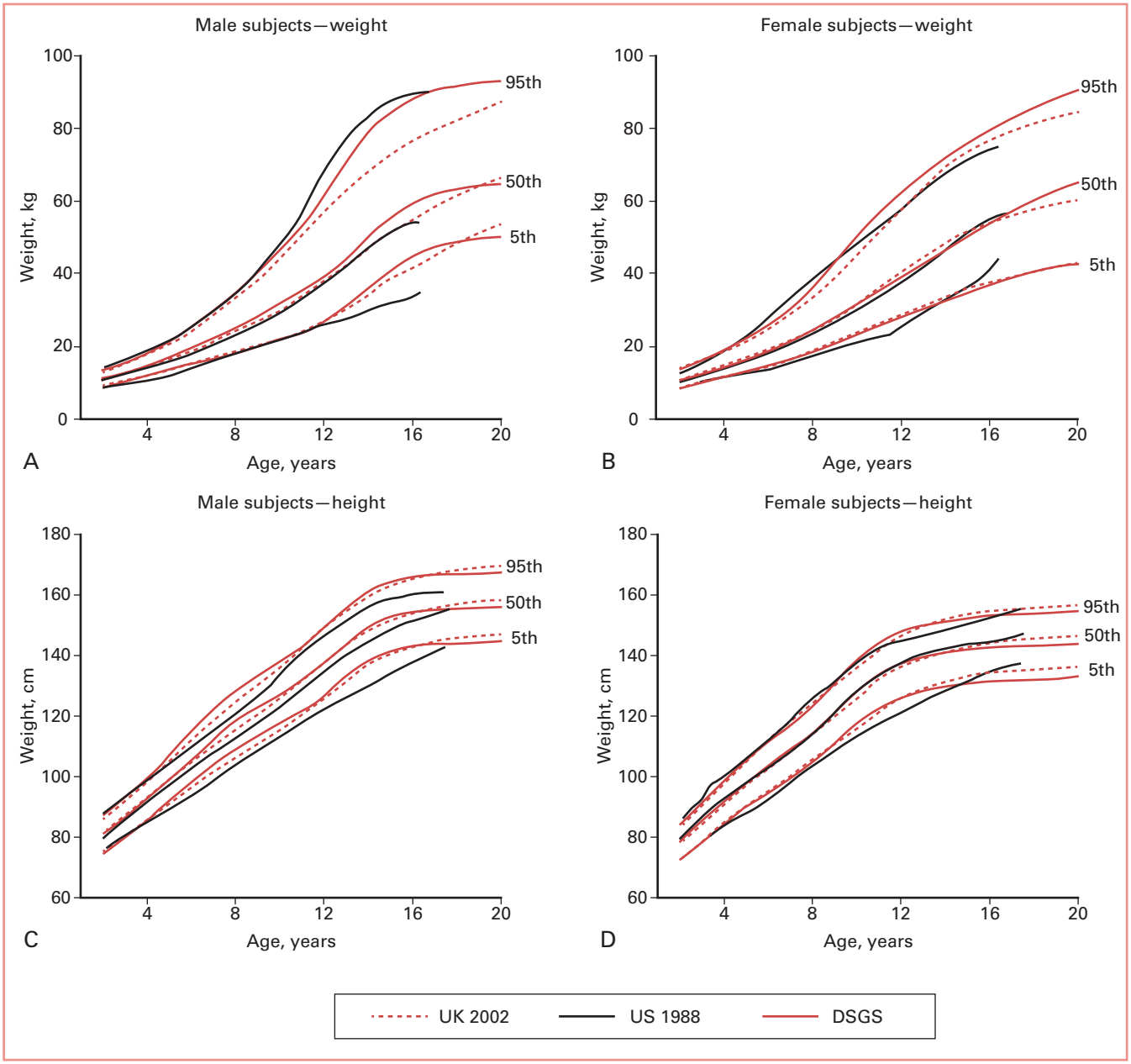

Figure 42.2. Curve comparisons for weight in kilograms and height in centimeters for male and female subjects, 2 to 20 years of age. Contemporary curves from the Down Syndrome Growing Up Study (DSGS [solid line]) are compared with those from the US 1988 curves from Cronk et al (dotted line) and the UK 2002 curves from Styles et al (dashed line).

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Laboratory Tests

Annual thyroid screening for thyroid-stimulating hormone and thyroxine levels is recommended for all school-age children and adolescents with trisomy 21, in addition to other routine screening tests. Hearing evaluation should also occur at least once in older children and annually thereafter. Because of the risk of keratoconus, an annual ophthalmologic consultation should be conducted after the age of 10 years. Additionally, the child with trisomy 21 should be encouraged to continue biannual dental visits, because gingivitis, periodontal disease, and bruxism (ie, teeth grinding) are common in these individuals.

Management

The major part of the visit with school-age and adolescent children should focus on developmental, educational, and vocational anticipatory guidance. Educational placement and future goals should be developmentally appropriate for the child and acceptable to the parent. Activities requiring socialization and development of

Box 42.3. Physical Examination of the Child With Trisomy 21

- Look for dry, sensitive skin and alopecia, which manifests in approximately 10% of children and resolves spontaneously.
- Monitor the size of the anterior and posterior fontanels, because delayed closure may be indicative of hypothyroidism.
- Check for visual abnormalities, such as strabismus, nystagmus, cataracts, refractive errors, and blepharitis.
- Document recurrent serous otitis media. It is estimated that 40%–60% of children with trisomy 21 have significant conductive hearing loss and 20%–30% have some degree of neurosensory loss.
- Examine the oropharynx carefully for delayed dentition, malocclusion, and caries.
- Auscultate for stridor, wheezing, or other abnormal breathing that may indicate airway anomalies.
- Perform a thorough cardiac examination and note any evidence of previously unrecognized congenital heart disease.
- Palpate the abdomen for distention or organomegaly. Children with trisomy 21 have a slightly increased risk of developing acute non-lymphoblastic or acute lymphoblastic leukemia.
- Perform a rectal examination in infants or children with a history of constipation.
- Evaluate any musculoskeletal abnormalities such as overall hypotonia and joint laxity (most commonly in the knees and hips) that might contribute to overall gross motor delay.

responsibility should continue to be encouraged; however, these events can be very stressful for parents and other family members. Injury prevention should be highlighted as well, especially because older children are becoming more independent. In early adolescence, prevocational and vocational training within the school curriculum should be reviewed. Additionally, brief discussions about independent living, group homes, transition of medical care, and financial resources (eg, community-supported employment for young adults) should begin during adolescence.

For older children and adolescents with trisomy 21, puberty, fertility, and contraception are extremely important issues to address with both the patients and their parents. The patient's psychosocial development and physical sexual maturation should be discussed, including menstrual hygiene and any foreseeable problems with its management. Contraception and the potential for victimization must be addressed as well, particularly with female patients. Males with trisomy 21 usually are sterile, but females have an approximately 50% chance of having children of their own with Down syndrome.

Prognosis

Individuals with trisomy 21 often can live well past the age of 50 years, unless they are born with a congenital heart lesion, which may limit life expectancy. One major cause of morbidity and mortality is the manifestation of symptomatic Alzheimer disease, which occurs in approximately 15% of adults after the fourth decade. Many adults with Down syndrome remain asymptomatic, however, despite histopathologic evidence of the disease.

CASE RESOLUTION

The family should be encouraged by the healthy progress of the patient. For this visit, anticipatory guidance should consist of a review of early intervention services, available resources, and general support services for the patient and her family. The increased risk for upper respiratory infections and otitis media should be reviewed. Medical screening should include thyroid screening, subjective hearing screening, and a formal evaluation by a pediatric ophthalmologist. If the results are normal, the next visit should take place 3 months hence.

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CHAPTER 43

Well-Child Care for Preterm Infants

Soina Kaur Dargan, MD, FAAP, and Lynne M. Smith, MD, FAAP

CASE STUDY

A 10-week-old girl was discharged from the neonatal intensive care unit 2 weeks previously, where she had resided since birth. She was the 780 g (27.5 oz) product of a 26-week gestation born via spontaneous vaginal delivery to a 32-year-old primigravida. The perinatal course was complicated by premature rupture of membranes and maternal amnionitis. Several aspects of the neonatal course were significant, including respiratory distress that required surfactant therapy and 2 weeks of endotracheal intubation; a grade 2 intraventricular hemorrhage diagnosed at 1 week after birth; hyperbilirubinemia, which was treated with phototherapy; several episodes of apnea, presumably associated with the preterm birth; and a history of poor oral intake with slow weight gain.

The parents have a few questions about her feeding schedule and discontinuing the apnea monitor, but they feel relatively comfortable caring for their daughter at home. She is feeding well (2 oz of 22 cal/oz postdischarge formula for preterm infants every 2–3 hours) and, according to the family, is becoming progressively more alert. She sleeps on her back in a crib.

The infant's weight gain has averaged 25 g (0.9 oz) per day. The remainder of the physical examination is normal, with the exception of dolichocephaly and esotropia of the left eye.

Questions

1. What constitutes well-child care in preterm infants?
2. What are the nutritional requirements of preterm infants in the months after discharge from the hospital?
3. What information must be considered in the nutritional assessment and developmental screening of preterm infants?
4. What immunization schedule is appropriate for preterm infants? Do they require any special immunizations?
5. What specific conditions or illnesses are more likely to affect preterm infants than term infants?

Preterm birth is defined as birth before 37 completed weeks of gestation. However, the increased frequency of adverse neonatal outcomes in neonates born at 37 and 38 weeks' gestation led the American College of Obstetricians and Gynecologists to redefine *optimal delivery* as 39 weeks' gestation to eliminate nonmedically indicated deliveries prior to this time. Because advances in neonatal care have resulted in improved survival, an increased demand exists for skilled primary care physicians who can care for the preterm infant. Providing primary care for these infants is an important and challenging task and often requires coordination of medical, developmental, and social services for multiple chronic conditions. Because preterm infants are at increased risk for impaired growth and developmental delay, longer well-child visits may be necessary to evaluate their nutritional and developmental progress and assess how families have adjusted to caring for them at home. Primary care physicians must learn to manage these and many other complex issues while providing families with comprehensive anticipatory guidance. Providing a medical home in which care is accessible, comprehensive, continuous, culturally sensitive, and family oriented is essential to the optimal heath and developmental outcome of the patient who was born preterm.

Epidemiology

In the United States, the Centers for Disease Control and Prevention (CDC) reports that preterm birth rates decreased from 2007 to 2014, in part because of a decline in the number of births to teenagers and young mothers. However, since 2016, preterm births are once again on the rise, the cause of which is largely unknown.

The preterm delivery rate is highest for black women and lowest for white women (14% and 9%, respectively). The increase in preterm births has occurred among late preterm newborns (>34 weeks' gestation), who comprise 70% of preterm births. Reasons for the increased preterm delivery rates include increased use of artificial reproductive technologies (see Chapter 26), increased interest in elective cesarean section, and increased maternal age.

Although most preterm newborns are delivered at greater than 34 weeks' gestation, these neonates are at increased risk for morbidity and mortality compared with neonates born at term. Additionally,

many neonatologists routinely resuscitate neonates born at 23 weeks' gestation, a gestation with a survival rate of approximately 25%. Very low-birth-weight (VLBW, <1,500 g [<52.9 oz]) and extremely low-birth-weight (ELBW, <1,000 g [<35.3 oz]) newborns are at risk for cerebral palsy, respiratory disease, hearing and vision problems, and intellectual disabilities. Furthermore, learning disabilities, attention-deficit/hyperactivity disorder, borderline to low IQ scores, psychiatric disorders or abnormalities in executive function, and visuomotor integration occur in more than 50% of VLBW infants, thereby complicating post-discharge care for these children. In 2007, the Institute of Medicine (now the National Academy of Medicine) estimated the annual societal cost of preterm birth at $26 billion and individual family cost of $2 million.

Pathophysiology

In utero, the placenta serves several functions, including promoting and regulating fetal growth, providing nutrients, and preventing infection by acting as a barrier. Delivery before 39 weeks of gestation halts this process, and these immature organs have functional limitations. Causes of preterm delivery can be maternal, the most common of which is pregnancy-induced hypertension, or fetal, the most common of which is premature rupture of membranes resulting from chorioamnionitis. Regardless of cause, these infants have special needs that should be addressed at every primary care visit.

Evaluation

The purpose of the health maintenance visit for preterm infants is the same as for other healthy children: to provide consistent preventive health care and education for patients and their parents. Preterm status, however, places children at risk for additional medical and neurodevelopmental conditions. Compared with children born full term, children born preterm have an average of nearly 3 times the number of well-child visits in the first year after birth and more hospital readmissions.

History

Almost one-third of preterm newborns are not brought in for their first scheduled outpatient appointment. Because failure to attend follow-up appointments has been associated with a higher rate of developmental delay, discussions about the importance of follow-up appointments are ideally initiated with the parent or caregiver before the infant is discharged from the neonatal intensive care unit (NICU).

It is imperative to review the entire medical history and hospital course before the initial visit and then discuss it with the family at the appointment. Ideally, the NICU should provide a discharge summary that includes the information listed in Box 43.1.

Any significant complications or concerns should be discussed with parents or caregivers at the earliest opportunity to assess their understanding of these issues and their expectations for improvement. Specifically, growth, nutrition, and developmental issues should be addressed at each visit (Box 43.2). Adequate or desirable weight gain should be explained to caregivers in terms of the infant's current weight versus discharge weight. Infants younger than 6 months should gain an average of 20 to 40 g (0.7–1.4 oz) per day. To ensure continued weight gain, many preterm infants are discharged from the NICU on a 24-hour feeding schedule, which requires that they be fed at least every 3 hours. The necessity for this practice should be reevaluated during the first few weeks following discharge after infants have demonstrated adequate weight gain.

Box 43.1. Neonatal Intensive Care Unit Discharge Summary Information

1. Birth weight, gestational age, and significant prenatal and perinatal information, including delivery room details
2. Overview of the hospital course by system, including significant illnesses, events, surgical procedures, and pertinent radiographic and other diagnostic studies
3. Nutrition information and present feeding regimen
4. A list of current medications, including dosing intervals and, if appropriate, the latest serum drug levels
5. Immunizations administered during the hospitalization
6. Pertinent laboratory and diagnostic data, such as most recent hemoglobin level, newborn screening results, ophthalmologic and hearing screening information, neurosonography and magnetic resonance imaging results, and highest serum bilirubin level
7. Discharge physical examination, including most recent height, weight, and head circumference
8. Parental or other social concerns throughout patient's stay in the neonatal intensive care unit
9. Problems remaining at discharge
10. All follow-up appointments

Box 43.2. What to Ask

Well-Child Care for Preterm Infants

- How much did the infant weigh when discharged from the hospital?
- Is the infant fed mother's milk, or is the infant formula-fed? Is the infant on any special formula?
- How often and how much does the infant feed? How long do feedings take?
- Does the infant have any feeding problems (eg, pain, vomiting, gastroesophageal reflux)?
- Does the infant take dietary supplementation of vitamins and minerals?
- What developmental milestones has the infant reached? Does the infant roll over? Smile? Sit up?
- Does the infant seem to hear and see?
- Who cares for the infant? Is the primary caregiver getting enough rest?
- Does the infant have regional services and if so, which ones and how often?
- Where and in what position does the child sleep?
- Does the parent or caregiver have any concerns about growth, development, or nutrition?
- Is the infant on an apnea monitor and/or caffeine? Has the infant experienced any apneic episodes?

Developmental history is a critical component of the health maintenance visit. Parental expectations and observations should be noted, and any developmental concerns should be evaluated. The adjusted developmental age should be calculated by subtracting the number of weeks the infant was born preterm from the infant's current chronologic age in weeks. The adjusted age should then be used for all formal and informal developmental assessments. The importance of correcting for preterm status until children are 2 years of age must be emphasized when discussing developmental progress and giving anticipatory guidance to parents or caregivers. It is important to know if the patient is receiving any regional services, which ones, and how often so an accurate recommendation can be made if it is necessary to increase these services.

Physical Examination

A complete physical examination should be performed at each visit to monitor the status of associated medical conditions. All growth parameters (ie, weight, height, and head circumference) should be plotted on the growth chart for preterm newborns until approximately 50 weeks' postmenstrual age and adjusted for preterm status on standard growth charts until age 2 years. Because catch-up head growth generally precedes catch-up weight and length, preterm infants may appear to have disproportionally large heads. The onset of accelerated head growth may begin within a few weeks after birth (36 weeks' postconception) or as late as 8 months adjusted age. Average daily weight gain in grams per day should also be calculated and discussed with the parent or caregiver at every visit.

The size and shape of the head must be evaluated, especially if the infant has a history of intraventricular or intracranial hemorrhage or hydrocephalus. An increase in head circumference of more than 2 cm (0.8 in) per week should be cause for concern in these infants. In infants who have undergone neurosurgical treatment for hydrocephalus, ventriculoperitoneal shunt and tubing may be palpated. The head must also be evaluated for *positional plagiocephaly*, a condition caused by lying in the same position for prolonged periods of time. Visual abnormalities, such as strabismus, must be carefully ruled out by both physical examination and history because up to 20% of preterm infants may have an ophthalmologic problem (see Chapter 91). Oropharyngeal abnormalities, such as a palatal groove, high-arched palate, or abnormal tooth formation, may occur as a result of prolonged endotracheal intubation. Baseline intercostal, substernal, or subcostal retractions; wheezing; stridor; and tachypnea in former preterm babies with moderate to severe bronchopulmonary dysplasia (BPD), a form of chronic lung disease, should be documented. Infants with BPD have increased susceptibility to pulmonary infections leading to rehospitalization and may continue to exhibit poor lung function through adolescence.

Chest and back scars secondary to the placement of chest tubes or patent ductus arteriosus ligation should be noted. Adult female breasts may be affected if scarring occurs on or close to breast tissue. The umbilicus may appear hypoplastic as a result of umbilical catheter placement and suturing. Scars on the distal extremities from intravenous catheters and cutdowns may be evident.

The genitalia of all preterm infants should be examined closely for inguinal hernias. Inguinal hernia repair is often deferred until 60 weeks' corrected gestational age unless incarceration risk is deemed high or the family lives far from a pediatric surgeon. Surgery is deferred because of concerns about adverse neurodevelopmental outcomes in children exposed to general anesthesia in the first months after birth, the high rates of postoperative apnea, and the occasional spontaneous closure in the first year after birth without intervention. If a hernia is surgically repaired under general anesthesia, the infant should be monitored for apnea for up to 24 hours postoperatively. The male scrotum should be examined for cryptorchidism, because at term gestation only 25% of testes are in the scrotum of males born preterm. By 1 year of age, more than 90% of testes are intrascrotal. A careful evaluation for developmental dysplasia of the hip should be performed until children are ambulatory, and hip ultrasonography (US) should be performed at 6 weeks of age for all breech deliveries (see Chapter 113).

A thorough neuromuscular examination is essential in children born preterm. Increased muscular tone, asymmetry, and decreased bulk should be noted along with the presence of any clonus or asymmetry of deep tendon reflexes. Inappropriate reflexes, such as a persistent Moro reflex or fisting beyond 4 months of age, should also be documented. Other abnormalities (eg, scissoring, sustained clonus) in the neurologic examination may become more apparent with age. The detection of subtle early findings is important so appropriate intervention services can begin as soon as possible.

Laboratory Tests

In addition to the standard screening tests performed on all healthy infants and children during health maintenance visits, several laboratory studies are important for preterm infants. Such tests include a hemoglobin test and reticulocyte count to assess for anemia; electrolytes in infants with BPD on diuretics to detect abnormalities; and serum calcium, phosphorus, and alkaline phosphatase levels in infants with documented metabolic bone disease of prematurity.

Pulse oximetry is indicated for oxygen-dependent infants as well as those presenting with respiratory symptoms greater than baseline. Results from newborn screening tests, including auditory and ophthalmologic examinations, should be reviewed and repeated as indicated. Cranial US should be reviewed with caution, because nearly 40% of infants born weighing less than 1,000 g (35.3 oz) with normal head US findings develop cerebral palsy or developmental delay. Additionally, infants with grade 1 or 2 intracranial hemorrhage are at increased risk for developmental delay. Brain magnetic resonance imaging should be considered in infants born at less than 30 weeks' gestation or in any infant with a concerning abnormal neurologic examination or abnormal rate of head growth.

Management

Well-child care in relatively healthy preterm infants has 2 components. One is the provision of routine health care maintenance for infants and appropriate developmental anticipatory guidance for

parents or caregivers. The other component involves the incorporation into each visit of treatment for chronic conditions that are sequelae of preterm birth. Health care maintenance should include the psychosocial well-being of the family, nutrition counseling, developmental surveillance, immunizations, and assessment of vision and hearing in addition to standard screening tests discussed previously. Outside resources concerning developmental delay can be reviewed with parents or caregivers. Care related to chronic conditions includes adjusting medication doses, such as diuretic therapy; weaning from supplemental oxygen; and discontinuing the apnea monitor.

Anticipatory Guidance

Before hospital discharge, parents or guardians should be given anticipatory guidance that caring for a NICU graduate is challenging (Box 43.3). The American Academy of Pediatrics (AAP) recommends parental education as 1 of 6 critical components of discharge planning for any high-risk neonate and includes not only educating parents about the patient's care but also identifying an additional caregiver who can assist with the demands of caring for the child at home. Preterm newborns have poorly organized sleep-wake cycles, resulting in more frequent awaking than term newborns. Additionally, preterm newborns have immature suck-swallow coordination, causing them to feed more frequently and for longer periods. Colic is reported twice as frequently in VLBW infants compared with infants born at term, and many are described as having difficult temperament until past their first birthday. Preterm infants also develop gastroesophageal reflux more often than full-term infants, which presents with such symptoms as irritability, respiratory problems, and postprandial vomiting.

The medical costs associated with the care of preterm infants often strain the family finances at a time when many women reduce their work schedules. Additional stressors include uncertainty about the long-term outcome of the child, guilt many women feel after delivering prematurely, and anxiety about future pregnancies. The difficulty of caring for these complicated, challenging children results in significant parental stress and can interfere with parents' ability to properly bond with their babies. Health professionals should be alert to signs of a parent feeling overwhelmed, because a higher caregiving burden is associated with an increased incidence of child welfare reports, such as child neglect.

Box 43.3. Physician Support and Education of Parents of or Caregivers for Preterm Infants

- Understand parental/caregiver expectations.
- Legitimize parental/caregiver fears.
- Be a source of support and encouragement.
- Provide consistent, honest information.
- Assume the role of the overall coordinator of care.
- Provide referrals to outside resources, including respite care.

Nutrition

According to the AAP Committee on Nutrition, the average daily energy requirement for most hospitalized healthy preterm newborns and infants is 105 to 130 kcal/kg/day to achieve adequate growth. Energy requirements vary by individual infant depending on associated chronic conditions, such as BPD or malabsorption. Key nutrients, such as calcium, vitamin D, and phosphorus, are critical to the management of bone health in preterm infants. Growth is considered adequate in the newborn weighing more than 2,000 g (>70.5 oz) if weight gain is more than 20 g (>0.7 oz) per day and length and head circumference increase 0.7 to 1.0 cm (0.3–0.4 in) per week. Feeding difficulties are common in preterm infants and result in hospital readmission secondary to failure to thrive.

At 40 weeks' corrected age, preterm newborns usually are smaller than term newborns. Adequate nutrition in the first year after birth is critical, because catch-up weight gain is unlikely to occur after age 3 years. Because human milk is insufficient for providing adequate protein and micronutrients to preterm newborns, fortifier is added to human milk.

If they are not receiving human milk, children born at 34 weeks or sooner or weighing less than 1,500 g (<52.9 oz) usually are discharged home on a nutritionally enhanced transitional formula (eg, Similac Expert Care NeoSure, Enfamil EnfaCare). The calcium, phosphorous, and caloric content of these 22 cal/oz transitional formulas are between levels found in standard preterm and term formulas. Use of preterm enriched formulas usually is continued until the child reaches the 5th to 10th percentile on the growth chart or is 1 year of adjusted age. A meta-analysis showed limited evidence to demonstrate that nutrient-enriched formulas improve growth rates after discharge relative to standard term formula.

Formula-fed infants require multivitamin supplementation until 750 mL/day of formula is consumed. Preterm infants fed mother's milk may benefit from continuing multivitamin solution and supplementation of oral iron drops as long as human milk is the predominant source of nutrition. Vitamin D supplementation is recommended for all infants fed mother's milk. Because preterm newborns are at increased risk for metabolic bone disease of prematurity, soy formulas are to be avoided because of the low phosphate content.

The introduction of solid foods is appropriate after an infant has developed acceptable oral-motor skills for swallowing solids. Recent studies have suggested that 20% of parents of preterm infants report feeding problems at age 2 years. Cow's milk should not be introduced until 12 months' adjusted age.

Developmental Surveillance

Informal and formal developmental surveillance should include referral to an early intervention program, particularly for ELBW infants, because routine screening tests are not sensitive enough to detect subtle neurodevelopmental abnormalities (Box 43.4; see Chapter 32). The Individuals with Disabilities Education Act Part C guarantees early intervention programs for infants and

Box 43.4. Typical Speech, Play, and Physical Development

In addition to standardized tests, the following guidelines provide development milestones useful for early detection:

By 3 Months' Adjusted Age, the Infant

- Coos or vocalizes other than crying
- Visually tracks a moving toy from side to side
- Attempts to reach for a rattle held above chest
- Pushes up on arms
- Lifts and holds head up

At 6 Months' Adjusted Age, the Infant

- Begins to use consonant sounds in babbling and uses to get attention
- Reaches for a nearby toy while on tummy
- Transfers a toy from 1 hand to the other while lying on back
- Reaches both hands to play with feet while lying on back
- Uses hands to support self in sitting
- While standing with support, accepts entire weight with legs

At 9 Months' Adjusted Age, the Infant

- Increases variety of sounds and syllable combinations in babbling
- Looks at familiar objects and people when named
- Explores and examines an object using both hands
- Turns several pages of a chunky book at once
- Imitates others in simple play
- Sits and reaches for toys without falling

At 12 Months' Adjusted Age, the Child

- Meaningfully uses "mama" or "dada"
- Responds to simple commands (eg, "come here")
- Produces long strings of gibberish in social communication
- Finger feeds self
- Uses thumb and pointer finger to pick up tiny objects
- Pulls to stand and cruise along furniture
- Stands alone and takes several independent steps

At 15 Months' Adjusted Age, the Child

- Has a vocabulary consisting of 5–10 words
- Helps with getting undressed
- Walks independently and seldom falls
- Squats to pick up toy

At 24 Months' Adjusted Age, the Child

- Uses 2- to 4-word sentences
- Walks up and down stairs holding on for support
- Builds a tower of 4 blocks or more
- Identifies basic body parts

Derived from Pathways Awareness Foundation. *Assure the Best for your Baby's Physical Development.* https://pathways.org/topics-of-development/milestones/ as well as Centers for Disease Control and Prevention. Developmental milestones. CDC.gov website. http://www.cdc.gov/ncbddd/actearly/milestones/index.html. Accessed July 16, 2019.

toddlers with disabilities up to age 3 years. Children born weighing less than 1,200 g (<42.3 oz) are automatically eligible, but any child with suspected developmental delay is entitled to an evaluation to determine eligibility for services regardless of a family's ability to pay. Because many developmental issues do not manifest until school age, frequent developmental assessments and enrollment in preschool are especially important for infants born preterm.

The AAP recommends that autism spectrum disorder (ASD)–specific screenings be completed for all childrenat 18 to 24 months of age. The prevalence of ASD has been reported to be 8% in children born at less than 26 weeks, which is much higher than that for the general population. Preterm newborns have higher scores on the Modified Checklist for Autism in Toddlers, with greater social-communication difficulties and autistic-like behaviors. These increased scores may be reflective of the increased incidence of neurodevelopmental delays in individuals born preterm, making screening for ASD more challenging.

Immunizations

Routine immunization schedules recommended by the CDC Advisory Committee on Immunization Practices should be followed. The administration of any vaccine is determined by the patient's chronologic or postnatal age, not gestational age. Standard doses and intervals should also be used (see Chapter 37). Several studies have shown an adequate serologic response despite a history of prematurity. Absolute and relative contraindications to specific vaccine components or to live vaccines for preterm infants are identical to published guidelines for term infants and children. In addition to following the recommendation that all infants 6 months and older be vaccinated against influenza, the pediatrician should strongly urge that all household contacts of preterm newborns be vaccinated. Two doses of influenza vaccine are administered 1 month apart, with subsequent immunization the following year requiring only 1 dose. Because the rotavirus vaccination utilizes a live virus, it is recommended only for clinically stable preterm newborns if they are 6 to 14 weeks' chronologic age at the time of hospital discharge or have already been discharged from the NICU.

If adequate weight gain has been established, it is safe to administer hepatitis B vaccine to medically stable infants weighing less than 2,000 g (<70.5 oz) as early as 30 days of age or at hospital discharge, whichever comes first. All neonates born to mothers who are positive for hepatitis B surface antigen should receive hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 12 hours of delivery. When maternal hepatitis B status is unknown, the neonate should be vaccinated for hepatitis B within 12 hours of birth. In this situation, if status remains unknown, the neonate weighing less than 2,000 g (<70.5 oz) should receive HBIG within 12 hours after birth and those weighing 2,000 g (70.5 oz) or more should receive HBIG within 7 days after birth.

The CDC recommends that all pregnant women receive the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine to help protect their newborns against pertussis. Maternal vaccination results in higher concentrations of pertussis antibodies in newborns compared with unvaccinated mothers, possibly resulting in increased protection against pertussis during the critical period

between birth and the first diphtheria and tetanus toxoids and acellular pertussis vaccine dose.

Because respiratory syncytial virus (RSV) causes increased morbidity and mortality in NICU graduates and infants with congenital heart disease, administration of the RSV-specific immunoglobulin palivizumab (eg, Synagis) is recommended every month from November through March (Table 43.1). A documented infection with RSV is not an indication to discontinue passive immunization, because multiple strains may circulate during the RSV season.

Assessment of Vision and Hearing

Follow-up visits for visual and auditory sequelae of prematurity must be arranged at the health maintenance visit. An initial ophthalmologic screening examination should have been performed between 4 and 9 weeks of age in infants weighing less than 1,500 g (<52.9 oz) or born less than 30 weeks' gestation, irrespective of oxygen exposure. Infants between 1,500 and 2,000 g (52.9–70.5 oz) or greater than 30 weeks' gestation with an unstable clinical course should also be screened. The frequency and need for repeat examinations are determined based on initial findings. Regardless of the presence of retinopathy of prematurity, preterm infants are at increased risk for strabismus, myopia, amblyopia, and glaucoma and must undergo an ophthalmologic examination between 4 and 6 months of age. Because birth before 28 weeks' gestation is associated with an increased risk of retinal detachment later in childhood and early adult life, long-term follow-up to detect and manage late-onset retinal detachment should be considered.

Table 43.1. Indications for the Use of Palivizumab for Respiratory Syncytial Virus Prophylaxis

Indication	*Age at Onset of RSV Season*
Preterm infant with chronic lung disease requiring medical management with oxygen, a bronchodilator, diuretics, and corticosteroids	<24 months
Hemodynamically significant congenital heart disease with cyanosis and moderate to severe pulmonary hypertension	<24 months
Significant congenital abnormalities of the airway or neuromuscular disease that compromises handling of respiratory secretions	<12 months
Born ≤28 weeks of gestation	<12 months
Born 29–31 weeks 6 days of gestation	<6 months
Born 32–34 weeks 6 days of gestation with at least 1 of 2 risk factors, whether attending child care or with a sibling younger than 5 years of age in the home	<3 months

Abbreviation: RSV, respiratory syncytial virus.

The AAP recommends universal hearing screening for all newborns. Neonatal intensive care unit graduates account for approximately 50% of all newborn hearing screening failures, and severe sensorineural hearing loss occurs in up to 10% of ELBW infants. Screening is recommended immediately before discharge, and repeat testing is recommended if the child develops speech delays.

Other Potential Problems

Preterm infants exposed to mechanical ventilation and prolonged exposure to oxygen are at risk for BPD. These infants are at increased risk for respiratory illness, especially during the winter. Parents or caregivers should be informed of this risk and counseled about symptoms such as tachypnea and wheezing associated with a simple upper respiratory infection. Physicians should have a low threshold for considering a diagnosis of pneumonia in these infants even in the absence of classical symptoms.

The primary care physician should also keep in mind that preterm infants are at increased risk for sudden unexpected infant death (SUID; see Chapter 72). The AAP recommends that all infants sleep in the supine position. In the NICU, neonates often are placed on their stomach if they have respiratory difficulties and on their side if they have symptomatic gastroesophageal reflux. Neonatal intensive care unit personnel need to begin placing these babies on their backs in anticipation of discharge. The physician should counsel the parent or caregiver about safe sleep practices, that is, placed on the back in a crib without blankets, pillows, or other objects. Parents and caregivers should also be reminded that bedsharing is not recommended and is highly associated with SUID from accidental asphyxia.

Home apnea monitors are not associated with the prevention of SUID and should be reserved for infants who are considered to have extreme cardiorespiratory instability or are being discharged on oral caffeine. Discontinuation of caffeine and home monitoring may be considered at 42 weeks' postmenstrual age and when significant apneic events have ceased, whichever comes later.

Preterm survivors who were critically ill can be particularly at risk for developing vulnerable child syndrome because their parents may continue to perceive them to be fragile and vulnerable. Features of this syndrome include abnormal separation difficulties for mother and child, sleep difficulties, parental overprotectiveness and overindulgence, lack of appropriate discipline, tolerance of physical abusiveness by the child toward the parent, and excessive preoccupation with the child's health. Serious behavioral problems may arise as a result of such parent-child interactions, and recent studies suggest a correlation between higher parental perception of child vulnerability and worse developmental outcomes. Primary care physicians must be cognizant of early signs of this syndrome and should try to prevent its occurrence by reassuring parents or caregivers about the child's well-being. After vulnerable child syndrome is suspected, connecting the child's history of critical illness with ongoing parental concerns is important because many parents are unaware that current concerns may stem from their unresolved anxiety. Every effort should be made to normalize the family's schedule after the

infant is stable and to encourage parent-child interactions unrelated to health care.

Prognosis

Neurodevelopmental impairment is a concern for physicians who care for preterm infants. Risk factors for developmental delay include postnatal steroid exposure, necrotizing enterocolitis, BPD, small for gestational age status, and maternal pregnancy-induced hypertension. Chorioamnionitis is a risk factor for cerebral palsy in term infants and possibly in infants born preterm. Extremely low birth weight infants and those born between 20 and 25 weeks' gestation are at significant risk for developmental issues. Surviving infants born at less than 26 weeks' gestation in the United Kingdom in 1995 had median Bayley mental and psychomotor scores of 80 at 30 months of age, with comparable cognitive score deficits at age 6 years and a higher prevalence of learning difficulties, including lower reading and mathematics scores at 11 years.

During adolescence, 50% of former VLBW infants have an IQ in an abnormally low range, and 30% have attention-deficit/hyperactivity disorder. Although individuals born preterm experience higher rates of chronic medical and neurodevelopmental problems, their self-perception of health and well-being in adolescence has been found to be the same as those of their normal birth weight peers. Additionally, increased systolic blood pressure, insulin resistance, and impaired glucose tolerance have also been reported in VLBW adults. Parents should also understand that long-term follow-up information may not accurately reflect the outcome for their child because these adolescents were treated before subsequent advances in prenatal and neonatal care.

CASE RESOLUTION

The current feeding schedule for the infant should be continued because appropriate weight gain has occurred. Iron and multivitamin supplementation is recommended until the infant is consuming 750 mL/day of formula. Discontinuation of the apnea monitor can be considered after the infant reaches term gestation (40 weeks) and has been event-free. The first set of immunizations should be administered at this visit, and any questions the family has should be answered. A follow-up visit should be scheduled for 3 to 4 weeks hence. Formal developmental testing should be arranged to take place in 1 to 2 months, and the parents should be encouraged to continue placing the infant on her back alone in her crib to sleep.

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CHAPTER 44

Care of Children With Special Health Care Needs

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CASE STUDY

A 5-year-old girl with a physical disability is brought to your office for her first visit for a routine physical examination for school entrance. She was the result of a full-term pregnancy complicated by an elevated screening α-fetoprotein and subsequent fetal ultrasonography that demonstrated a lumbar myelomeningocele and no hydrocephalus. Delivery was by elective cesarean section, with an Apgar score of 9 at both 1 minute and 5 minutes, to a 25-year-old gravida 1, para 0–1 mother. The mother used no illicit drugs, alcohol, or any other medications during pregnancy but was not on vitamins or folate supplementation at the time of conception. At delivery, a low lumbar spinal malformation was noted, with no other malformations. The quadriceps muscles were strong, but the feet demonstrated a rocker-bottom deformity.

Shortly after birth, the myelomeningocele malformation was closed by neurosurgery. Later, the girl underwent orthopedic surgical release of Achilles tendon contracture and currently is ambulatory with the use of ankle-foot orthoses. She has a neurogenic bladder and requires intermittent catheterization. She also has chronic constipation that is managed with a bowel regimen. Her cognitive function is age-appropriate.

She will be entering a school program for the first time since moving to this community and has not established care with any specialists.

Questions

1. Why is early identification and intervention important for newborns, infants, and children with special health care needs?
2. What role do primary care physicians play in the care of children with special health care needs?
3. What are the appropriate referrals and resources for families of children with special health care needs?
4. What specific psychosocial issues should be addressed whenever children with special health care needs visit their primary care physician?

Children and youth with special health care needs (SHCN) have physical, developmental, emotional, or behavioral conditions that require special health-related services. These conditions must last longer than 1 year and result in 1 of 5 consequences: the need for prescription medications; the need for increased medical care; compromised mental health or limited educational ability; the need for special therapy; or the need for counseling. Children with SHCN are defined by the International Classification of Functioning, Disability and Health as *disabled* if they are limited from doing what children of the same age can do. Most information on children with SHCN combines the group with and the group without disabilities. Conditions experienced by children with SHCN can range from mild to severe, depending on the nature and extent of them and their effect on daily living. Frequently, care requirements of families and health professionals for children with a diagnosis of SHCN are dramatically increased. For parents, the diagnosis of a condition in their child can be initially overwhelming and disappointing. Support of the parents is essential as they transition from disappointment to acceptance and assume the role of facilitator of their child's treatment plans.

Early identification of a health condition by a physician can result in appropriate, definitive treatment of many diagnoses. In some instances, early intervention may even prevent secondary conditions (eg, early management of hearing loss with hearing aids may minimize speech abnormalities). Even when such corrective treatment is not available, prompt identification improves children's long-term outcome and allows families to obtain appropriate resources for their children. Through early intervention, newborns, infants, and children with irreversible conditions can be introduced to medical, educational, and psychosocial services available in the community that serve to help these children maximize and reach their full potential.

Epidemiology

According to a national survey, an estimated 11.2 million children in the United States have SHCN, affecting 23% of households with children across all racial, ethnic, and socioeconomic groups. Approximately 65% of children with SHCN reportedly have more than 1 medical condition, including attention-deficit/hyperactivity

disorder, asthma, autism spectrum disorder (ASD), cerebral palsy, developmental delay, diabetes, and epilepsy. A single sensory disability, such as deafness, affects approximately 3.5% of children; blindness occurs in 1% of children. The prevalence of cerebral palsy is 1.5 to 2 per 1,000 live births. Advances in medical technology, as well as improved survival of low-birth-weight newborns and children with malformations, have increased the number of children living with such disabilities. Environmental exposures have increased the incidence of chronic medical conditions, such as asthma.

The presence of SHCN has a profound effect on the health and education of affected children. Studies show that children with SHCN have 1.5 times more doctor visits and spend 3.5 more days in the hospital than children without these conditions. Children with SHCN miss twice the number of school days and are twice as likely to repeat a grade compared with children without medical conditions.

In addition, numerous associated conditions occur more commonly in children with SHCN. These include intellectual developmental disorders, growth failure, and nutritional problems. Problems with dentition, respiratory infections, and bowel and bladder continence also may occur. Significant emotional disturbances may occur as children adapt to their condition.

Clinical Presentation

Children with SHCN can present in a variety of ways depending on their diagnosis. Many physical disabilities may be readily apparent at birth on the newborn examination or newborn screening. Some diagnoses, such as cerebral palsy, may be detected later, as the motor impairment becomes more evident. Following the child's development at routine health maintenance visits is essential for early detection of developmental delay. Implementing the Bright Futures program from the American Academy of Pediatrics (AAP) can help in early detection of many conditions. Children with SHCN also may present with chronic illness (eg, asthma, diabetes) or with specific complaints (eg, poor vision or hearing). Alternatively, they may present with a more general concern, such as growth failure (Box 44.1). Behavioral problems or difficulties in school may precipitate the initial visit.

Box 44.1. Diagnosis of Children With Physical and Sensory Disabilities[a]

- Growth failure
- Microcephaly
- Abnormal neurologic examination, including hypertonicity, spastic diplegia or quadriplegia, and brisk deep tendon reflexes
- Developmental delay
- Speech or hearing deficit
- Visual deficit
- Physical malformations

[a] May not be present in all children.

Pathophysiology

Pathophysiology of a medical condition is completely dependent on the specific diagnosis. Conditions may be secondary to an embryologic defect such as myelomeningocele, or to an infection such as congenital cytomegalovirus (CMV), which interferes with cochlear development and results in hearing loss. Etiologies are often multifactorial. For some conditions, such as ASD, the pathophysiology is unknown and may have several different etiologies.

Special health care needs may be classified as acquired or congenital and static or progressive. *Cerebral palsy*, for example, is a group of nonprogressive neuromotor disorders resulting from a central nervous system insult prenatally or within the first 2 years after birth. It is characterized by abnormal motor movements and posturing and may be accompanied by other problems as well. Causes of cerebral palsy include preterm birth, low birth weight, asphyxia, prenatal abnormalities (eg, placental insufficiency), congenital infections (eg, toxoplasmosis, CMV), and biochemical abnormalities (eg, severe hyperbilirubinemia). Other causes are environmental (eg, in utero exposure to alcohol) and genetic (eg, inborn errors of metabolism). Severe postnatal injuries or infections also may result in cerebral palsy (eg, abusive head trauma, meningitis). However, an estimated 25% to 50% of cases of cerebral palsy have no discernible cause.

Diagnosis

The term *SHCN* is used in a broad sense to include conditions that require additional medical care and supervision, as defined by the US Department of Health and Human Services Maternal and Child Health Bureau. As previously noted, children with SHCN may have significant physical, sensory, or developmental disabilities that may result from preterm birth, congenital infections (eg, CMV), or exposure in utero to alcohol or illicit substances. Some children are born with congenital malformations or inborn errors of metabolism that mandate special diets and occupational or physical therapy. Other children with SHCN include those with chronic medical conditions, such as asthma, obesity, and sickle cell anemia. All these medical conditions alter lifestyle, require increased medical care (including subspecialty care), increased medication usage, and increased use of community services compared with the general pediatric population.

Evaluation

History

When initially evaluating children with newly diagnosed SHCN, health professionals should first determine any specific parental concerns. A complete medical history should be obtained, including information about the pregnancy and birth. The history also should include any possible exposures as well as significant infections. General screening questions about development are important to ask to assess the child's developmental progress (Box 44.2). Specific questioning is warranted if parents are concerned about delayed development or if any of their responses

Box 44.2. What to Ask

Children With Special Health Care Needs

- Were there any perinatal complications, such as premature rupture of membranes or fetal distress?
- Was the child born prematurely? If so, how long did the child remain in the hospital and for what reasons?
- Was the child exposed to any toxins (eg, alcohol, illicit drugs) in utero?
- Is there any history of infection during the perinatal period or infancy?
- What developmental milestones has the child mastered?
- Is the child attending school or some type of early intervention program?
- How does the child get there?
- What does the child do on returning from school?
- Who feeds and bathes the child?
- Can the older child use the toilet without assistance?
- How is the child sleeping? Does the child take naps at school and home?
- Has respite care been arranged for the family?
- Does the caregiver seem overwhelmed or excessively tired, especially one who is caring for a child with multiple disabilities?
- Do other family members help care for the child?
- Is extended family available to help with siblings?
- Are there any other people with disabilities in the family?
- Does the family receive any financial assistance for care of the child?

indicate that their child is not attaining age-appropriate developmental milestones.

In cases of children with known sensory or physical disabilities, families should be asked directly at each visit about daily activities and the child's ability for self-help skills. Because many children with disabilities are also on daily medication for seizures or other chronic conditions, it is important to ask about the presence of any drug side effects.

Any behavioral or emotional problems in the child should be identified. Additionally, an overall assessment of family dynamics should be made. It is important to inquire about the relationships between children with SHCN and their siblings, as well as the effect these children have on the parents' marriage or relationship.

Physical Examination

In general, a complete physical examination, including an oral health assessment and a detailed neurologic assessment and neuromotor examination, should be performed at each visit. Height, weight, and head circumference should be plotted on the growth chart and compared with previous measurements. Failure of adequate growth as measured by any of these parameters should be examined closely. For example, microcephaly, nutritional problems, and growth failure are not uncommon in children with cerebral palsy. Depending on the specific diagnosis, the examination should focus on physical findings associated with the particular condition. For children with physical disabilities such as congenital or acquired amputations, for instance, assessment of the skin that comes in contact with prosthetic devices is a pertinent aspect of the physical examination. Pressure sores may be found in nonambulatory children with cerebral palsy. In children with sensory disabilities, such as unilateral hearing loss, the evaluation of middle ear effusion or infection in the unaffected ear should be prioritized. If a child has a tracheostomy or gastrostomy tube, inspection of the site is essential at each visit to look for erosions or skin infections.

Overall, for most children with SHCN, the neurologic examination is extremely important (Box 44.3). An age-appropriate developmental assessment is also an essential part of the examination at all health maintenance visits.

Laboratory Tests

Laboratory evaluation of newborns, infants, and children with physical or sensory disabilities depends on their specific conditions. Not all patients need a costly array of diagnostic procedures. A chromosomal karyotype or comparative genomic hybridization using peripheral blood is helpful in children with suspected genetic disorders (eg, abnormal facies, a major anomaly, developmental delay). Routine testing for fragile X syndrome should be strongly considered in all boys with intellectual and developmental disabilities and in girls with a family history of it. Other testing should be specific for the suspected diagnosis (see Chapter 84).

Metabolic screening for inborn errors of metabolism should be performed on children with intellectual and developmental disabilities and any of the following symptoms: intermittent vomiting or lethargy, loss of developmental milestones, or seizures. Such screening is not needed in the routine evaluation of children with developmental delay and no other symptoms.

A screening test for visual acuity (Snellen eye chart) and hearing (ie, audiogram) should be performed in all children with suspected sensory deficits, even mild ones. For infants and toddlers, a brain stem auditory evoked response or behavioral audiogram is a more appropriate screening test for hearing (see Chapter 88). A visual evoked response can be performed to test vision.

Psychometric testing may be helpful in certain school-age children to assess intellectual function. Electroencephalography is indicated in all patients with a history of seizures or seizure-like episodes.

Imaging Studies

Brain imaging studies, such as magnetic resonance imaging of the head, can be informative in the setting of suspected intrauterine infection, intraventricular hemorrhage, or genetic disorders with

Box 44.3. What to Ask

Neurologic Examination of the Child With Special Health Care Needs

- Are normal primitive reflexes (eg, Moro, rooting) present in neonates?
- Do newborns and infants appear to visualize and track objects appropriately?
- Are there any abnormal movements of the trunk or extremities at rest?
- Is muscle tone normal?
- Is any hypertonicity or hypotonicity evident?
- Is any asymmetry of the upper and lower extremities apparent?
- Are deep tendon reflexes normal and symmetrical?
- Have all primitive reflexes been extinguished in older children?
- Is the gait appropriate for age?

associated developmental delay and even isolated global developmental delay. Electromyography can be used to differentiate cerebral palsy from a congenital myopathy.

Management

Caring for children with SHCN can be rewarding yet challenging for primary care pediatricians. The pediatrician should be cognizant that these patients will take increased practice time and paperwork to ensure that they receive all services necessary. Case management services are an essential aid to their management. The primary care pediatrician must supervise acute and chronic medical care, provide anticipatory guidance, monitor growth and development, coordinate subspecialty involvement, make educational referrals, and offer community services. Sometimes a subspecialty physician will provide comprehensive care if the diagnosis (eg, cystic fibrosis) encompasses most of the child's health care needs. Although care should be individualized to each patient, general guidelines have been developed for the provision of pediatric services to newborns, infants, and children with SHCN. The guidelines include recommendations for establishing a medical home with the primary care pediatrician, medical services, suggestions for parental involvement, assistance from community agencies, and fulfillment of specific federal requirements for educational opportunities for children with disabilities. Pediatricians who care for children with SHCN should be familiar with the principles of care published by the AAP and should incorporate these principles into the overall treatment plan. Pediatricians also should be knowledgeable about the rights of such individuals as established by various legislation, including the Americans with Disabilities Act and the Individuals with Disabilities Education Act Part C. Coordination of intervention services and the use of adaptive or assistive technology are essential components of management.

General Considerations

The major role of primary care pediatricians who care for children with SHCN is 4-fold: provide primary medical care; serve as the patient and family advocate in evaluating therapeutic options; inform families of available community resources; and most important, serve as a proactive coordinator of care. The first task of the pediatrician is to establish the diagnosis and recognize any comorbidities. Whether the diagnosis is an obvious physical malformation or one that is not readily apparent, physicians are placed in the challenging position of breaking the news to families. Parents should be informed of the diagnosis as soon as possible, but care should be taken to refrain from discussing the prognosis, especially if it is still unknown. The cause of any disability and the possible complications of the condition should be reviewed with parents. *The primary goal is to help children with disabilities reach their full potential.*

Health professionals are in a unique position to establish a treatment plan with families that includes medical, psychosocial, and educational services. A multidisciplinary team should be assembled that includes the pediatrician, a member of the school system, a social worker, and a representative of an early intervention program. Federally funded, nonprofit, regional centers can provide an organized treatment plan and entry into an early intervention program to some children with disabilities. To qualify, children must be diagnosed with an eligible condition, such as cerebral palsy, epilepsy, ASD, or global developmental delay. In addition, newborns and infants considered to be at risk for developing disabilities qualify for assistance (eg, preterm newborns with bronchopulmonary dysplasia and intraventricular hemorrhage). For children who do not qualify, similar services can be coordinated on an individual basis by the physician's office or the school district.

Children with severe physical and sensory disabilities often are cared for by many medical subspecialists in addition to the primary care pediatrician. Referrals to pediatric orthopedic surgeons, plastic surgeons, geneticists, ophthalmologists, otolaryngologists, child neurologists, and psychologists may be necessary. Special comprehensive clinics, such as those for craniofacial or spina bifida, are established in some children's referral centers to facilitate care of patients, with multiple subspecialists forming a multidisciplinary team in the same clinical setting. In addition, speech and language, occupational, and physical therapists are often an integral part of the medical team. Initial and ongoing therapeutic services provided by each of these individuals must be monitored periodically to assess the progress and overall effectiveness of the treatment plan. Ideally, services should be coordinated so that children and parents miss a minimum number of school days and workdays (eg, Saturday and after-school appointments, visits to several practitioners on the same day). All information from diagnostic studies and initial evaluations should be shared among each of the health professionals. The AAP has produced a *Building Your Medical Home* toolkit (https://medicalhomes.aap.org), which can be very helpful to the primary care pediatrician.

The primary care physician also should offer counseling to parents on ethical issues pertaining to their child's condition. These issues include palliative care decisions, decision making in critical care situations, limiting nonbeneficial interventions at the end of life, and advance directives. Because of the pediatrician's relationship with the family, that physician may be in the best position to engage parents in conversations concerning these topics. Coordinated conferences with the primary care physician, specialists, social workers, and the family may be effective in counseling.

The family has a vital role in caring for the child with SHCN, and that care can frequently be stressful and emotionally draining. Family support and counseling should be readily available. The sociocultural context of the family and needs of any other children in the family should be considered when the care of the child with SHCN is addressed.

With improved medical care and services, 90% of children with SHCN reach adulthood. Transition into adult services can be challenging. Preparation for this transition should begin as early as 11 years of age to ensure success. The goal should be independence to the degree that is possible. The individual should be prepared for a work environment, if possible, and financial independence. The family and child should be evaluated to determine whether the child is capable of independent living or will need support in a group home or an institution or to remain with the family. If necessary, guardianship issues must be addressed. A successful transition to adult

health professionals must be ensured, and insurance coverage must be arranged. The Patient Protection and Affordable Care Act of 2010 has greatly improved insurance coverage for these patients, including extending the age of coverage for dependent children until age 26 years, preventing exclusion from coverage based on preexisting conditions, and prohibiting lifetime caps on medical expenses.

Psychological Concerns

Children with SHCN have more mental health issues than their peers. These conditions include behavioral problems, depression, anxiety, low self-esteem, peer relationship problems, school performance problems, and absenteeism. Children with SHCN that include a disability have even higher rates of psychological comorbidity. It is important that primary care physicians screen for these disorders and refer patients for counseling when appropriate.

Economic Concerns

The cost of care for children with SHCN is a significant financial burden for as many as 40% of these families in the United States. Families with an affected child are more likely to have a single income, have a single parent, live in poverty, and have poor-quality housing. Economic evaluation should be performed by caseworkers to determine the eligibility of children with SHCN for financial support through Supplemental Security Income and medical insurance under Medicaid. Caseworkers can help families apply for the appropriate assistance or to other programs, such as the Supplemental Nutrition Assistance Program and the Low Income Home Energy Assistance Program, which can help extend a family's resources.

It is apparent that children with SHCN from low-income families have reduced access to health, educational, and social services. Recent studies have been undertaken to determine the best strategy to improve access to services and availability of services for underserved communities. Early intervention services can reduce the economic burden of these patients and their families.

Specific Medical Conditions

Several medical conditions commonly occur in children with moderate to severe disabilities. While providing children with comprehensive well-child care, general pediatricians also can address and manage these conditions.

Problems with adequate nutrition, which usually result from insufficient caloric intake, manifest in the form of growth failure. Depending on the degree of disability and extent of oropharyngeal dysfunction, the placement of a nasogastric or gastrostomy tube may be necessary. Caloric needs may be 10% to 50% higher than that of children without SHCN.

Respiratory illness is not uncommon among children with SHCN. Close observation and conservative management of viral illnesses are often necessary. Aspiration pneumonia is likely to occur, especially in children with severe developmental delay resulting from poor handling of oral secretions or severe oral dyspraxia. To help minimize respiratory infections, these children always should be administered influenza vaccine during the winter months.

Maintaining good oral hygiene is another challenge, because some children with disabilities do not clear oral secretions well and retain food in their mouths, predisposing to cavity development. In addition, many children are treated with anticonvulsant agents and antibiotics that can cause gingival and enamel dysplasia. Abnormal oromotor coordination, tone, and posturing also contribute to the development of oropharyngeal deformities, such as high-arched palate and overcrowded teeth. As with other children, fluoride supplementation and consistent preventive dental care are recommended.

Bowel and bladder continence is important to attain for several reasons. It allows children to function in a socially acceptable fashion, provides independence, and prevents the development of complications such as recurrent urinary tract infections, diaper dermatitis, and decubitus pressure sores. Behavior modification techniques coupled with positive reinforcement are associated with the complete or partial success of bowel training.

Community Resources

Optimal care for children with SHCN depends on maximum use of community agencies and resources. An assessment of parental and patient needs should first be performed and prioritized. The appropriate resources should then be identified for individual children. Early intervention services should be used. Primary care physicians may need to help determine the appropriateness of specific services for patients and families. Emphasis should be placed on integrating each child into support services. Parent-to-parent support and sibling support groups can be quite helpful in relieving stress, helping parents understand the diagnosis, and avoiding feelings of isolation. Support groups for siblings as well as parents are available. Respite care to give parents a break from caregiving and in-home health service programs also should be investigated. In-home hospice care is available for children near the end of life; it can be an excellent support for the patient and family. Physicians should act as liaisons between all agencies. Case conferences are occasionally necessary to review the progress of individual children with each member of the health care team.

Education

By federal law, every child with a disability is entitled to an education. Every effort should be made to enroll children with disabilities in conventional schools and provide opportunities for socialization at an early age. Structured independence and mainstreaming children with disabilities in classes with children without disabilities can be quite productive for all the children involved regardless of disability status.

Mainstreaming may not be available in some areas, and the severity of some disabilities may preclude attendance at a regular school campus. Several other educational possibilities can be considered, and each case should be evaluated on an individual basis. Options include special education classes in designated schools (full- or part-time attendance), special education classes in regular schools (full- or part-time attendance), a mix of part-time special education classes and part-time regular classes, or homeschooling. The

decision can be facilitated through the development of an Individualized Education Program by a multidisciplinary team at the school. Parents and primary care physicians are encouraged to participate in this evaluation (see Chapter 36).

Prognosis

The prognosis for children with SHCN is dependent on the diagnosis, the severity and extent of any disability, medical and supportive intervention, and the child's environment. It may be impossible to establish a prognosis at the time of diagnosis. Children may adapt differently to the same diagnosis. It is important to establish realistic goals to determine the best intervention. With comprehensive care, many affected children can lead productive, independent lives, and maximal potential can be realized in all cases.

CASE RESOLUTION

Although the girl's medical condition of low lumbar spina bifida seems stable, the physician should inquire about any ongoing problems or concerns. A complete examination should be done. Routine screening laboratory tests and immunizations required for school entry should be performed. The family should be evaluated for financial stability and support services. The mother should be placed on folate supplementation for prevention of recurrence in future children. The patient should be referred to the local spina bifida clinic for comprehensive specialist care by orthopedists, urologists, and physical therapists. Integration into the regular classroom should be recommended. The school should be contacted to arrange for adaptive physical education and for intermittent catheterization by school nursing personnel. A follow-up visit is scheduled with the primary care physician in 2 months to review the child's integration into services.

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CHAPTER 45

Injury Prevention

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CASE STUDY

A 16-year-old girl was brought to the emergency department after being rescued from her submerged vehicle. The girl was texting a friend while driving and crashed into a pond. After several weeks in the intensive care unit, she was transferred out for rehabilitative care from her injury.

Questions

1. How pervasive are childhood injuries?
2. What are different approaches to injury prevention? How could this particular injury have been prevented?
3. What is TIPP and how should it be used when counseling families?
4. What are some general guidelines for effective injury prevention counseling?
5. How does a child's age affect the advice offered to a family?

Traditionally, unintentional injuries have been called "accidents." The problem with this term is that it implies unpredictability, carrying with it connotations of chance, fate, and unexpectedness. The perception that injuries are chance occurrences that cannot be predicted or prevented has been a major barrier to progress in injury prevention and the study and control of injury as a scientific discipline. According to the modern view of injury, accidents must be anticipated to be prevented. Specialists in injury prevention have tried to replace the word *accident* with *injury* and have developed the idea of reducing injury risk. Thus, injuries are not random events at all; they occur in predictable patterns determined by identifiable risk factors. For example, if a 16-year-old is texting while driving, which has been shown to be a dangerous driving distraction, the resulting injury can hardly be called an accident. On the contrary, the injury is entirely predictable.

Epidemiology

Unintentional injuries are the leading cause of death among people aged 1 to 44 years in the United States. In 2016, unintentional injuries claimed the lives of more than 18,000 Americans 21 years and younger. Suffocation is the third leading cause of death among newborns and infants; drowning is the leading cause of death among 1- to 4-year-olds; and motor vehicle crashes are the leading cause of death among 5- to 21-year-olds. Fires and burns are another major cause of unintentional injury-related death in young people.

Intentional or violence-related injuries are also a major cause of mortality in young people. Suicide is the second highest cause of death among 10- to 21-year-olds. Homicides are the third highest cause of death among 15- to 21-year-olds and fourth highest cause of death among 1- to 14-year-olds. Most suicides and homicides are firearm related.

In addition to deaths, in 2016, nonfatal injuries led to almost 9 million hospital emergency department visits in people younger than 21 years in the United States. The most common causes of nonfatal injuries in children are falls, followed by injuries from being struck by or against something, overexertion, motor vehicle occupancy, cuttings/piercings, and bites/stings.

Several epidemiological factors are associated with higher rates of pediatric injuries, including sex, race, income status, and family stressors (eg, death in the family, new residence, birth of a sibling). There is a bimodal age distribution of injuries, with newborns/infants and adolescents at greatest risk. Males are more likely than females to die from injuries and slightly more likely to experience injuries. Females are more likely than males to experience sexual assault. American Indian/Alaska Native and black children have higher rates of total injury-related deaths than other racial and ethnic age-matched populations. Geography influences injury rates; drowning deaths tend to be higher in coastline states (ie, Alaska and California) or states with a higher number of swimming pools (eg, Texas), and injury-related deaths are higher in rural areas and may be related to decreased access to emergency medical care.

Strategies for Injury Prevention

Efforts to prevent injuries have shifted from changing the behavior of individuals to modifying the environments in which injuries occur. William Haddon, MD, a medical epidemiologist, devised 2 useful frameworks for developing injury prevention strategies: the Haddon matrix and a list of 10 countermeasures to prevent injuries or reduce the severity of their effects.

Haddon Matrix

This matrix relates 3 factors (host, vector, and environment) to the 3 phases of an injury-producing event (pre-event, event, and post-event). The 3 factors interact over time to produce injury. Table 45.1 shows

Table 45.1. The Haddon Matrix Applied to Motor Vehicle Crash Injuries

Phase	*Host (Human)*	*Vector (Vehicle)*	*Environment*
Precrash	Driver vision Driver impairment (eg, alcohol, drugs) Distracted driving (eg, telephone, text)	Brakes Tires Speed Crash avoidance equipment and technology	Speed limit Road curvature Road signs
Crash	Use of safety belts Use of age-appropriate car safety seats	Vehicle size Airbags	Median barriers Laws about use of car safety seats and safety belts
Postcrash	Age Physical condition	Fuel system integrity	EMS personnel training

Abbreviation: EMS, emergency medical services.

Adapted from the National Committee for Injury Prevention and Control. Injury prevention: meeting the challenge. *Am J Prev Med.* 1989;5(3 suppl):1–303.

a Haddon Matrix of motor vehicle crash injuries. The precrash phase describes elements that determine whether a crash will occur; the crash phase describes the variables that influence the nature and severity of the resultant injury; and the postcrash phase describes the factors that determine the degree to which the injury is limited and repaired after the crash occurs. By describing the "anatomy" of an injury, the Haddon Matrix illustrates the numerous characteristics that determine an injury and the many corresponding strategies for interfering with the production of an injury.

Haddon's list of 10 countermeasures to prevent injuries or reduce the severity of their effects are as follows:

1. Prevent creation of the hazard (eg, stop producing poisons, toys with small parts, and non-powder firearms; do not participate in dangerous sports; support community centers that engage children in safe after-school activities).
2. Reduce the amount of the hazard (eg, package drugs in nonlethal amounts; reduce speed limits).
3. Prevent the release of the hazard (eg, use child-resistant caps for medications, toilet locks, and safety latches on cabinets and drawers; pass and enforce distracted driving laws; implement restrictions on handgun purchases; counsel families who keep guns to store them unloaded in a locked case, with the ammunition locked separately).
4. Modify the rate or spatial distribution of release of the hazard (eg, require airbags in cars; use child safety seats and safety belts; make poisons taste bad).
5. Separate people from the hazard in space or time (eg, make sidewalks for pedestrians, bikeways for bicyclists, and recreation areas separated from vehicles).
6. Separate people from hazards with material barriers (eg, use bicycle helmets and protective equipment for athletes; install fences around swimming pools; build window guards).
7. Modify relevant basic qualities of the hazard (eg, place padded carpets under cribs; require guns to have safety locks; develop inter-vehicle communication systems).
8. Increase resistance to damage from the hazard (eg, train and condition athletes; make structures more earthquake-proof; use flame-retardant sleepwear).
9. Limit the damage that has already begun (eg, use fire extinguisher; begin cardiopulmonary resuscitation).
10. Stabilize, repair, and rehabilitate injured individuals (eg, develop pediatric trauma centers and physical rehabilitation programs; improve emergency medical services).

Haddon's work serves as a practical guide for thinking about ways to prevent injury. It emphasizes the importance of considering injuries as a result of a sequence of events, with many opportunities for prevention. The shift of emphasis away from changing human behavior to preventing injury is particularly appropriate for injuries in children because inhibiting children's curiosity is impractical as well as undesirable.

Passive and Active Interventions

Interventions to prevent injuries can also be categorized as passive or active. *Passive* or *automatic strategies* protect whenever they are needed, without the action of parents or children. An example is the automobile airbag that automatically inflates to cushion occupants during a crash. Other examples of automatic strategies are water heater temperatures set to 48.9°C (120°F) or lower, not having guns in the home, and the use of energy-absorbing surfaces under playground equipment. In contrast, *active interventions* require action to become effective, such as in the case of nonautomatic safety belts, which require individuals to "buckle up" every time they enter an automobile. Supervision of swimming children is another example of an active injury prevention strategy.

Some strategies are partially automatic, requiring some action by individuals. Smoke detectors can be very effective in preventing injury and death in house fires, but roughly one-third of smoke detectors do not have working batteries. Batteries should be changed once a year and ideally tested once a month. As might be expected, the greater the effort required for children to be protected, the smaller the chance that protection occurs. Therefore, whenever possible, passive measures are preferable because they are the most effective.

Several approaches have been used successfully to prevent childhood injuries, including engineering, education, legislation, and enforcement. An engineering intervention, the car safety seat, is extremely effective (Table 45.2). When used correctly, child safety seats in passenger cars reduce the risk of death by 71% for infants and 54% for toddlers aged 1 to 4 years. Booster seats reduce injury risk by 59% for children aged 4 to 7 years compared with safety belts alone. Unfortunately, studies indicate that between one-third and two-thirds of car safety seats are used incorrectly. To address this, newborn care units often have car safety seat education programs, and some require possession of an infant car safety seat prior to hospital discharge. Police departments and private motor companies hold free public events to teach and manually check appropriate

Table 45.2. Pediatric Car Safety Seat Guidelines[a]

Age Group	*Type of Car Safety Seat*	*General Guidelines*
Term newborns/ infants	Rear facing	Rear facing as long as possible, until they reach the highest weight or height allowed by their seat.
Toddlers/ preschoolers	Rear facing and forward facing	Rear facing as long as possible. All children who have outgrown their rear-facing seat should use a forward-facing seat with a harness until they reach the highest weight or height allowed by their seat.
School-age children	Belt-positioning booster seat	When weight exceeds limit for car safety seat. Use until adult safety belt fits correctly (usually at 4′9″ and between 8 and 12 years of age).
Older children	Safety belts	When old enough and large enough to use the vehicle safety belt alone.

[a] All children younger than 13 years should be restrained in the rear seats of vehicles.
Adapted from Durbin DR, Hoffman BD; American Academy of Pediatrics Council on Injury, Violence, and Poison Prevention. Child passenger safety. *Pediatrics.* 2018;142(5):e20182460.

car safety seat use. In addition to engineering and education, passage and strict enforcement of child restraint laws are essential to compliance. All 50 states and the District of Columbia have child restraint laws (www.iihs.org/topics/seat-belts#laws). Nevertheless, loopholes still exist, such as exemptions in some states for safety belt use if older children are riding in rear seats; for safety belt use in school buses, taxis, and police vehicles; and if all safety belts are already in use. Such exemptions reinforce parental misconceptions, particularly that the lap of an occupant (ie, the "child crusher" position) is a safe position.

Counseling by Pediatricians

Although the existence of significant gaps in parental knowledge about injury prevention has been clearly established, studies have shown that pediatricians spend surprisingly little time counseling parents about childhood safety. One survey found that only 42% of caregivers of children younger than 15 years who had a medical visit in the past year recalled receiving injury prevention information. Another survey found only 15% of patients presenting with an unintentional injury reported receiving injury prevention counseling. Reasons for limited discussion of safety issues may include lack of emphasis on preventive medical care in medical schools and pediatric training programs, inadequate time or payment, and lack of perceived self-efficacy or effectiveness. Research, however, has shown that injury prevention counseling in primary care settings is effective, resulting in increased knowledge and improved safety practices. Parents report that they would listen to physicians much more than any other group about child safety.

TIPP—The Injury Prevention Program was developed in 1983 by the American Academy of Pediatrics (AAP) to firmly establish injury prevention as a cost-effective standard of care for pediatricians. The AAP suggests that health professionals focus their safety counseling on a few topics targeted to individual risk factors (eg, age, sex, location, season of the year, socioeconomic status of family). Table 45.3 shows the age-specific counseling schedule of TIPP, which indicates the minimum topics to cover at each visit. Specific preventive measures should be reinforced at each visit. Areas of injury prevention guidance recommended for adolescents include traffic

Table 45.3. TIPP—The Injury Prevention Program Safety Counseling Schedule for Early and Middle Childhood

Visit	*Introduce*	*Reinforce*
Birth–6 months	Rear-facing car safety seat, fall risks, burn prevention, smoke alarm use, choking/ suffocation prevention	Safe sleep
6–12 months	Drowning prevention, poisoning risks, strangulation hazards	Safe sleep, rear-facing car safety seats, fall risks, burn prevention, smoke alarm use, choking/suffocation prevention
1–2 years	Firearm hazards	Poisoning risks, fall risks, burn prevention, smoke alarm use, drowning prevention, rear-facing car safety seats
2–4 years	Play equipment safety	Fall risks, firearm hazards, burn prevention, smoke alarm use, poisoning risks, car safety seats
5 years	Bike safety, street safety, water safety, fire safety	Firearm hazards, car safety seat or belt-positioning booster seat and safety belt use
6 years	Safe swimming	Fire safety, firearm hazards, bike safety, street safety, water safety, car safety seat or belt-positioning booster seat and safety belt use
8 years	Sports safety	Water safety, bike safety, firearm hazards
10 years	"Rules of the road" while biking	Firearm hazards, sports safety, water safety, safety belt use, bike safety

Adapted from the American Academy of Pediatrics Council on Injury, Violence, and Poison Prevention. *TIPP—The Injury Prevention Program: A Guide to Safety Counseling in Office Practice.* Itasca, IL: American Academy of Pediatrics; 2019

safety (eg, safety belts, alcohol use, motorcycle and bicycle helmets), water safety (eg, alcohol use, diving injuries), firearm safety, sports safety, and distracted driving.

Connected Kids: Safe, Strong, Secure is a violence prevention tool introduced by the AAP in 2006 to augment TIPP. Acknowledging that injury and violence prevention are intertwined, it uses an asset-based approach to engage parents in understanding and fostering healthy child development. An emphasis is put on support and open communication to promote emotional and physical safety.

Health professionals should involve parents and patients in educational efforts (eg, have a bicycle helmet in the office for children to try on). Safety counseling is most effective if limited to 2 or 3 topics per visit. Advice should be well defined and practical rather than general information (eg, write the Poison Help number on the phone; never leave children unattended in water). Advice should be tailored to each family after exploring individual situations through open-ended questions (eg, "Where does your baby spend awake time during the day?"; "What do you think is the biggest safety risk for your child?"). Health professionals should be aware of different levels of health literacy and confirm understanding rather than rushing through a prepared statement. Access to interventions should be considered, such as cost and accessibility of helmets and child safety seats. Whenever possible, pediatricians should coordinate their educational efforts with current community injury prevention efforts (eg, bicycle helmet campaigns, handgun regulation).

Recent Recommendations

The AAP has multiple safety recommendations. Following are newer and revised recommendations:

- Health equity is fundamental to child safety. Children should be protected from injury within their built environment and provided with access to quality, patient-centered, and culturally effective medical care (Reaffirmed 2013).
- All children should be restrained in a rear-facing–only or convertible car safety seat used rear facing as long as possible. Importantly, nearly all currently available convertible car safety seats have weight limits for rear-facing use that can accommodate children 35 to 40 lb (15.9–18.1 kg) (2018).
- Motor vehicle crashes are the most common cause of mortality and injury for adolescents and young adults in developed countries. Now present in all 50 states, graduated driver's license programs introduce driving in a staged manner of increasing risk and responsibility. The AAP recommends that pediatricians know their state laws addressing teenage drivers, encourage seat belt use, help parents identify acute or chronic medical or behavioral risk factors that might affect their teenager's driving ability, discourage distracted driving, encourage restrictions on nighttime driving and limits on number of passengers, and counsel teenagers about the dangers of driving while impaired (2018).
- Research suggests both benefits and risks of media use for the health of children and teenagers. Parents and pediatricians can work together to develop a Family Media Use Plan (www.healthychildren.org/MediaUsePlan) that considers children's developmental stages to individualize an appropriate balance for media time and consistent rules about media use (2016).
- Pedestrian injuries are a significant traffic-related cause of morbidity and mortality. Emphasis should be given to community- and school-based strategies to reduce exposure to high-speed and high-volume traffic, and to promote improvements in vehicle design, driver manuals, driver education, and data collection to reduce pediatric pedestrian injury (Reaffirmed 2019).
- The absence of guns from homes and communities is the most reliable and effective measure to prevent firearm-related injuries in children. The AAP supports a number of specific measures to reduce the destructive effects of guns, including the regulation of the manufacture, sale, purchase, ownership, and use of firearms; a ban on semiautomatic assault weapons; and the strongest possible regulations of handguns for civilian use (Reaffirmed 2016).
- Drowning is a leading cause of injury-related death in children. Pediatricians should provide specific targeted messages by age, sex, risk of drowning, alcohol or drug use, water competency, and geographical location. Children with special health care needs should have tailored anticipatory guidance related to water safety (2019).
- Injury is the leading cause of death in children 1 to 18 years of age in the United States. The unique needs of injured children must be integrated specifically into trauma systems and disaster planning at the local, state, regional, and national levels. Pediatric injury management should include an integrated public health approach from prevention through prehospital care, to emergency and acute hospital care, to rehabilitation and long-term follow-up, as indicated (2016).
- Children exposed to intimate partner violence are at an increased risk of being abused and neglected and are more likely to develop adverse health, behavioral, psychological, and social sequelae later in life. It is recommended that pediatricians receive training on the identification, assessment, and documentation of abuse; interventions to ensure patient safety; culture and values as factors that affect intimate partner violence; applicable legal responsibilities; and violence prevention (Reaffirmed 2019).
- The overall death rate attributable to sleep-related infant deaths remains high. Recommendations for a safe sleep environment include supine positioning, the use of a firm sleep surface, room sharing without bed sharing, and the avoidance of soft bedding and overheating (2016).
- Sport-related concussions are a major health concern in young athletes. Although all concussions cannot be prevented, reducing the risk through rule changes, educational programs, equipment design, and cervical strengthening programs may be of benefit. Health care professionals should have an understanding of their individual state's laws regarding return to play after a concussion (2018).

Additional policies and guidelines can be found at www.aappublications.org/search/%20subject_collection_code%3A100 using the key words "injury prevention."

Pediatricians as Advocates

As advocates for child safety, pediatricians can play a major role in injury prevention outside the clinical setting. Pediatricians have started community programs or provided support to ongoing programs. Safe Kids Worldwide (www.safekids.org) is an organization made up of safety experts, educators, corporations, foundations, governments, and volunteers whose mission is to prevent childhood injury through education and advocacy. Safe Kids and other issue-specific organizations, such as the Children's Defense Fund (www.childrensdefense.org) and Everytown for Gun Safety (https://everytown.org), can provide resources to support pediatricians in local or national projects and provide avenues for legislative participation. Through community pediatrics programs (www.aap.org/commpeds), the AAP provides grants to pediatricians and pediatric residents who want to create innovative community projects promoting child health.

Legislative advocacy is an exciting opportunity for health professionals to effect wide-reaching change. States have enacted laws covering many aspects of injury prevention, including car safety seats, poison centers, cribs, playgrounds, amusement parks, protective gear for sports, swimming pools, and school buses. Dramatic reductions in injuries often follow safety legislation. For example, infant walker-related injuries have decreased by 76% since the introduction of the ASTM International F977 Consumer Safety Performance Specification for Infant Walkers in 1997 and the introduction of stationary activity centers as alternatives to mobile infant walkers. Other examples of product-related legislation include federal crib standards of 1974 mandating close spacing of vertical slats to reduce the risk of entrapment, the Child Safety Protection Act of 1994 requiring toy safety labels on any balls with a diameter less than 1-¾ in (4.44 cm), window blinds manufactured with tassels instead of loops and children's clothing without drawstrings to prevent strangulation, and toy boxes manufactured with safer lids and air holes in case a child is trapped within. Similarly, in December 2010, the US Consumer Product Safety Commission voted to ban drop-side cribs, citing the recall of more than 9 million cribs over the previous 5 years and the entrapment and death of 30 babies over the previous 10 years. The ban went into effect in June 2011 and prohibits the sale of such cribs even at garage sales.

Pediatricians can heighten awareness about the magnitude of childhood injuries through calls or letters to legislators, testifying about the benefits of specific safety legislation, or partnering to introduce new legislation. Pediatrician legislative involvement is critical to ensuring evidence-guided local and national injury prevention.

CASE RESOLUTION

Your experience with this case prompts you to become more involved in advocacy about adolescent drivers and accident prevention. You have the opportunity to engage families in injury prevention as well as to influence the individuals who manufacture the products and pass the laws that affect children's risk of injury.

Some of the factors that influenced the injury and outcome include a significantly increased risk of fatal crash for adolescent drivers, evidence that graduated driver licensure laws and other restrictions on young drivers reduce deaths, passage and enforcement of laws pertaining to cell phone use in cars, vehicle design, road conditions, availability of emergency rescue services and access to specialized pediatric care, and pediatrician counseling to caregivers and adolescents advocating family driving rules.

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CHAPTER 46

Fostering Self-esteem

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CASE STUDY

A 4-year-old girl is brought to the office for her annual physical examination. She has been healthy. The mother is concerned that her daughter is shy and does not seem eager to play with other children. She does not attend child care or group activities outside the home, and she spends most of her time with her mother, grandmother, and 7-year-old sister, with whom she gets along well. Both parents work outside the home.

The girl's medical history is unremarkable with the exception of an episode of bronchiolitis at 8 months of age. She has reached all her developmental milestones at appropriate ages, speaks clearly in sentences, can dress herself without supervision, and can balance on 1 foot with no difficulty.

Her physical examination is entirely normal. At times during the visit, her mother sharply tells her to "Sit up straight," "Stop fidgeting," and "Act your age." The mother rolls her eyes as she says, "She doesn't know how to act."

Questions

1. What is self-esteem?
2. How do parents or other caregivers affect the development of their child's self-esteem positively and negatively?
3. What role does discipline play in the development of self-esteem?
4. How does illness affect self-esteem?
5. What suggestions can primary care physicians give parents and other caregivers to help foster positive self-esteem in children?

A mother worries about her spouse's sarcasm with their son. A father worries that indiscriminate praise at school inflates his child's sense of her abilities while setting her up for "a rude awakening." As the pediatrician walks into an examination room, a parent whispers that he wants to discuss their child's obesity away from the child. An urgent care visit is scheduled to discuss the persistent bullying of a child in school. Embedded in these scenarios and countless others is a concern that a child's self-esteem is malleable and fragile and that its preservation is crucial to a child's success. What should a primary care pediatrician know about how a child's self-concept affects the child's thoughts, feelings, and behavior?

Basic Concepts

Parents often use the term "self-esteem" to describe their child's confidence, implying a sense of agency and feelings of self-worth. In fact, *self-esteem* is a social psychological construct; it is the product of how an individual understands the effects of that individual's actions (ie, agency) and how the individual believes those actions are seen by others (ie, self-worth). *Agency*, or *self-efficacy*, is a child's confidence in his, her, or their capacity to successfully complete tasks or accomplish goals. *Self-worth* is the assessment that what a child thinks, wants, and does is important. High self-esteem often is accompanied by a sense of self-respect, purpose, and self-awareness, whereas low self-esteem typically is associated with self-questioning, defensiveness, and disproportionate self-criticism, even when receiving positive feedback. Although it may be most apparent in moments of achievement, self-esteem is also demonstrated by confidence that difficulties, failures, and disappointments are tolerable and can be accommodated. Self-esteem is essential to a child's well-being and influences the development of relationships and identity during childhood and adulthood. It is grounded in the fact that success with other people is fundamental to a sense of who we are.

Whether a child's self-estimate is inflated, overly negative, or accurate is not of importance to the concept of self-esteem; no "objective yardstick" exists. In this regard, it is important to understand that a difference exists between high self-esteem and narcissism. A child can have a healthy self-regard without a sense of entitlement, grandiosity, or feelings of superior worth. This distinction is important when critically reading research finding correlations between bullies and high self-esteem, for example; studies also find high self-esteem in those who intervene on observing bullying behavior. Alternatively, a child's disfigurement or disability should not preclude that child from possessing feelings of positive self-esteem. Self-esteem is a phenomenologic construct, and its importance lies in how a child's self-concept shapes that child's actions.

Self-esteem requires the development of certain cognitive abilities, but it is also based on experiences with parents, peers, and other caregivers. Preschool-age children become much more independent and spend more time away from primary caregivers compared with younger children. This newly acquired independence, however, does not remove the need for attention, interest, and approval from their parents. Agency must be nurtured, and not simply controlled,

to support self-esteem. Opportunities to demonstrate the competence of children can be recognized in the autonomy that appropriate parenting supports and heard as a source of pride in parents taking note of it. Educating parents about what is developmentally correct can be important. Competent play among preschoolers, for example, may involve playing alongside other children and may not necessarily consist of cooperative play (eg, helping each other in addition to playing together).

The emergence of self-esteem can be framed in terms of Erik Erikson's conceptualization of a child's social development. In the "industry versus inferiority" stage, the task of a child is to demonstrate the child's efficacy and for those efforts to be acknowledged and appreciated. The joy of autonomy and initiative are suffused with a need to live up to expectations; for example, for a young daughter part of feeling that she is a big girl is feeling that she is a good girl. The first stirrings of conscience and confidence to manage measured responsibility occur in this stage. The complex interaction of temperament, developmental stage, family security, parental style of discipline, sibling and peer interactions, and school experiences coalesce in the experience of a uniquely competent child. For her caregivers, the desire to encourage a kind of fearlessness is balanced by the very real need to keep the child safe and appropriate. All these aspects of her life contribute to the development of her competence, autonomy, and relatedness and animate her self-esteem. The development of self-esteem can be seen when children at the age of 5 years begin to experiment with identity roles, when they demonstrate an awareness of social comparison at age 7 or 8 years in their peer play and activities, and most clearly when they develop a sense of global self-esteem at approximately 8 years of age. Research also concludes that a general decline in self-esteem occurs from childhood through adolescence. It has been suggested that social comparisons and increased awareness of the perspectives of others cause adjustments to a growing child's self-efficacy and self-worth. This is intensified during adolescence, when physical changes and increased academic and social complexity test children's sense of who they are.

Much of a child's self-concept is established and reinforced by those around them, especially primary caregivers. Although important activities occur when the child is alone and engaged in individual pursuits, much of a child's self-concept develops in a context of relatedness. This extends beyond the family during school years, when peers and teachers assume a more influential role in the continued development and reinforcement of self-esteem. The development of self-esteem is transactional, built by the responses children receive to their increasing initiative and abilities, resting on a foundation of security. A secure interpersonal environment is essential to exploration and correction. This transactional nature is at the core of self-esteem interventions and their enthusiasm for effects on individuals as well as society.

All parents hope that their children will develop a positive self-concept that will aid them throughout their lives. Unfortunately, discussions related to self-esteem usually are held as a result of a crisis or an observation by worried parents or teachers. Primary care physicians should bring the parent's or parents' focus to this important aspect of their child as a normal part of anticipatory guidance. Pediatricians and health professionals are uniquely positioned to offer specific recommendations for fostering self-esteem that may affect the lives of their patients. During health maintenance visits with the child, these health professionals should model respect for the child's self-concept and highlight the growing capabilities found in the child's interactions.

Research

Research on self-esteem examines *global self-esteem*, that is, a measure of the overall assessment of the self, and *domain-specific self-esteem*, that is, measures of self-assessment related to performance and attributes (eg, academic competence, physical appearance). The most widely used measure for self-esteem, the *Rosenberg Self-Esteem Scale*, assesses global self-esteem. One difficulty in the self-esteem literature is that interventions meant to address specific performance areas are sometimes assessed with global self-esteem measures and vice versa. It is no surprise that a child's general sense of self is insufficient to improve the child's performance on a spelling quiz.

Some proportion of self-esteem is biologically rooted. Twin studies indicate that approximately 40% of variability in self-esteem can be explained by genetic factors. However, self-esteem also is known to have cultural underpinnings that seem to especially resonate in contemporary American culture. Whether the prominence of self-esteem is somehow rooted in the US national identity is unknown, but it is clear that the importance of self-esteem is not universally shared in all populations. For example, it is hard to detect self-esteem as a motivating factor in more collectivist cultures, such as Japan. This stands in broad contrast to its importance in US classroom reform or claims by psychologists first introduced in the 1990s that "self-esteem has profound consequences for every aspect of our existence." The proper conceptualization and importance of self-esteem remains a matter of debate.

At first glance, it would appear that an association exists between level of self-esteem and important health outcomes. Credible research concludes that high self-esteem predicts decreased rates of depression and increased happiness. Adolescents with high self-esteem have better mental and physical health as well as higher graduation rates and are less likely to have a criminal record. Higher self-esteem predicts improved persistence when confronting failure. Lower levels of self-esteem are associated with increased rates of obesity, drug abuse, and tobacco use. It is uncertain, however, whether the demonstrated outcomes associated with levels of self-esteem are caused by those levels of self-esteem. For example, researchers are still trying to determine whether self-esteem results in higher performance or better performance results in higher self-esteem. Causation can also be considered in the context of known correlations between self-esteem and academic performance and motivation, task performance, aggression, sex and/or gender differences, ethnic differences, and health outcomes.

Whether interventions promoting enhanced self-esteem result in improved outcomes is debatable. Research seems to have tipped the scales toward benefit from such programs when the programs include 3 specific elements: attributional feedback (ie, helping children attribute outcomes to effort), goal feedback (ie, promoting realistic, attainable goals), and contingent praise (ie, praise based on effort and improvements in performance). This seems to underscore the central importance of examining domain-specific interventions and self-estimation.

Parental Guidance

Illness and Difficult Family and Social Challenges

Physical and psychiatric illnesses threaten children's sense of who they are, undermining their self-efficacy and self-worth. Children can be left uncertain of their standing, expecting failure or feeling that they are inferior. Opportunities may exist for trusted physicians to help affected children and their families find realistic, achievable goals that affirm the children's sense of agency. It is often beneficial to help a child and family shift the narrative away from preexisting ideals and toward what is possible and of value.

A child's self-esteem can be particularly vulnerable in certain social and familial situations. A child may respond to negative experiences in school or at home with feelings of shame and worthlessness. Marital conflict, divorce, or the abuse of a parent may negatively influence the self-esteem of children who may feel complicit in or responsible for the problem. In such circumstances, parents are often concerned about the effect on the child, which provides an opportunity to work together to minimize negative effects. Honest, open communication between the physician and the parent or parents reinforces the need for sensitive support of the child and helps the parent or parents set priorities or rehearse how they will talk with the child about a given social or familial situation. (For in-depth discussion of divorce in particular, see Chapter 149.)

The issue of self-esteem is important in the context of managing "new morbidities." The diagnoses of obesity, attention-deficit/hyperactivity disorder, and learning disabilities can have in common the taint of personal judgment and the threat of undermining self-worth. Frank language that is sensitive to a child's self-esteem has a role in the disclosure of diagnosis, in addressing the reactions of both parent and child, in determining a realistic treatment plan, in acknowledging the frustrations and shame that come with slow progress, and in the framing of ultimate outcomes. Parents and patients will benefit from careful modeling by the pediatrician of how to represent and talk about the problem.

In the clinical setting, it can be challenging to provide practical advice that reflects research in this area. One helpful model for understanding self-esteem is the *self-determination theory*, in which a child's general self-concept is understood as an organization of complex, hierarchically interrelated components. Self-esteem is the evaluative aspect of self-concept and is linked to intrinsic motivation. Research has demonstrated that optimal challenges, effectance-promoting feedback, and freedom from demeaning critique; parenting that promotes autonomy rather than control; and a secure interpersonal environment of relatedness are all essential contributors to intrinsic motivation and, by extension, self-esteem.

Optimal Challenges

Successful parenting creates opportunities for children to safely extend their boundaries while ensuring their feeling of personal control. An overly critical or controlling style of parenting constrains the emergence of a child's young sense of competence and, by extension, affects the child's self-esteem. Being handed a scribble drawing by a preschooler and told what it represents is emblematic. An appreciative, interested, positive response to the disordered marks is sustaining, whereas disinterest and immediate correction or criticism is undermining. Inconsistent or harsh parenting and authoritarian as opposed to authoritative parenting styles detrimentally affect levels of self-esteem.

It may be important to discuss the difference between encouragement and pressure with parents, and many parents may benefit from an introduction to the concept of "positive communication." To support positive self-esteem, children need encouragement at all levels of their development (Box 46.1). This is communicated verbally and nonverbally and should be distinguished from overt pressure. For example, a first grader learning to spell should be praised for early, if flawed, application of phonemes, such as spelling "winter" as "wntur," and may not need correction at that point. Generally, children should be given room to experiment and develop at their own rate and should not be coaxed into activities before they are ready or judged too harshly for earnest, early attempts.

When pressure occurs, it may be the result of parents having unrealistic expectations of how a child learns and develops or an improper sense that lack of success is caused by laziness or a character flaw. Inadvertent pressure can be detrimental and can cause tremendous frustration when, for example, a parent tries to lead a toddler into toilet training when the child has shown few signs of readiness. Pressuring young children to give up pacifiers or another security object without giving thought to the child's readiness may also be quite anxiety provoking to them.

Box 46.1. Encouraging Self-esteem

Don'ts

- Have negative expectations.
- Focus on mistakes.
- Expect perfection.
- Overly protect children.

Dos

- Show confidence in children's abilities.
- Build on children's strengths.
- Value children as they are.
- Stimulate independence.

Children may not know what is best for their ultimate development, but well-intentioned pressure can be harmful as children grow older. Forcing children to participate in rigid, structured play and, sometimes, classes or lessons does not foster individual creativity or independence. The acquisition of technical skill is only part of learning, and the absence of intrinsic motivation can lead the child to feel that the effort is meaningless or inauthentic. Children ought to, but should not merely, do what parents have arranged. Encouragement to explore and occasionally take risks should build on their "islands of competence" or areas of strength. Mistakes should be put into the context of a sincere effort and understood in terms of what can be learned rather than as a humiliation. Pressuring children to do things "right" or "perfectly" discourages normal, healthy, risk-taking effort and can hinder future participation in activities unless they are certain they can succeed.

A variation on this theme is *overprotection*, in which the parent controls the child's environment to reduce any risk of failure or discomfort to the child. This generally comes at the cost of sacrificing the experience of novel achievement and developing the competence to work through frustrations and disappointments. Indiscriminate, unanchored praise is a corollary to this. Parents should be cautioned against always speaking in the superlative to their child and avoiding acknowledgment of any shortcomings. Children are adept at seeing the world as it is. A failure to see themselves reflected realistically by parents or caregivers may feed a sort of insecurity in which despite the glowing language of parents, the children feel uncertain of their actual worth. It robs children of opportunities to make accommodations. Both overprotection and indiscriminate, unanchored praise have a negative effect on self-esteem.

Effectance-Promoting Feedback and Freedom From Demeaning Critique

Specific means of communication that support self-esteem include active listening, use of positive language, discarding "labels," use of encouragement rather than pressure, and use of the "I" method of communication (Box 46.2). The pediatrician can coach parents that a child's behavior should not be expected to follow a rigid code of conduct at all times, but rather that the goal is a "good enough" environment in which well-intended parents make a consistent effort to be mindful of how they interact with their children. A useful way to set the correct tone with parents and caregivers is with the application of strength-based counseling, in which advice grows out of a focus on what parents are doing right.

Box 46.2. Communication That Builds Self-esteem

- Active listening
- Use of positive language
- Discarding "labels"
- Use of encouragement
- Use of the "I" method of communication

The purpose of active listening is to hear the child's message and understand its meaning. The success of active listening rests on a centered approach to important parenting moments; parents should strive to be attentive and present at these moments. They should stop what they are doing and look directly at their children. They should be aware of nonverbal cues, such as body posture and facial expression. If children are having trouble understanding their feelings, the parent should repeat what they hear them saying, for example, "It sounds like...."

A nonjudgmental response that is validating and nondismissive should be the goal of communication between primary caregivers and children. The basic message should be stated simply, clearly, and at a level that respects the maturity of the child. Words should be easily understood and spoken in a moderate tone, especially in cases in which discipline is necessary. Facial expression and body language should also be consistent with the message parents or caregivers are trying to convey.

Many parenting courses teach primary caregivers to use the "I" method of communication, which requires that parents explain their feelings to children rather than blame them for their actions. This approach is believed to be less threatening and demeaning for children, especially in situations requiring discipline. The "I" method has 4 recommended steps: statement of behavior or situation to be addressed (eg, "When you..."); statement in specific terms of how one feels about the effect of the situation on oneself (eg, "I feel..."); statement of reason (eg, "Because..."); and statement of expectations (eg, "I would like...," "I want..."). Using this approach, a parent might state, "When you speak so unkindly, I feel upset because I would never speak with you in that way. It makes you seem like the kind of person that you are not. I would like you to speak with me in the way we all try to speak with you, no matter how angry you feel."

Parents should be encouraged to reflect on the complex relationship between discipline and self-esteem, and they should be questioned about their impressions of their child's independence and competence. Promoting the growth of healthy autonomy should be a goal for all parents. As children grow, so too does their ability to act responsibly and maintain greater self-control. This central insight is an important means of helping parents conceptualize discipline as more than simply punitive.

The poorer outcomes associated with authoritarian parenting underscore the importance of positive language, even when disciplining children (see Chapter 50). For instance, when children are playing kickball in the house, it is understandable that a parent might yell, "Don't play ball in the house!" or "Haven't I told you before? No ball playing inside!" Although emotionally honest parenting in a loving context is the best parenting, parents should be mindful of when they are speaking in a reprimanding and negative fashion or transmitting their frustration. Parents or other adults should attempt to tell children clearly what they can do, what the limits are, and the reason for these rules. For example, a calm, more positive response might be, "You have to stop playing ball right now. If you kick the ball inside, you may break a window or hurt yourself or someone

else. You may kick the ball outside in the backyard." Communicating in a clear manner changes the tone of the interaction from a reprimand for being bad to one in which rules are clarified to a child who wants to do the right thing.

Parents should praise their children for successes and achievements. Failures should be put into context whenever possible, although the acknowledgment of mistakes can be important. A forgotten jacket or a careless job with homework can be frustrating, but neither is worthy of a demeaning critique. Negative labels have no helpful role. If children hear themselves referred to pejoratively by their primary caregivers, not only is an undesirable behavior modeled, but they will feel undermined and wonder about the truth of such statements, no matter how innocuous they may initially seem to parents.

Promoting Autonomy

Children do best when they are provided with clear, consistent guidelines for their behavior while simultaneously being encouraged to do well, pursue their interests, and increase their abilities. They are more likely to achieve autonomy when they see this behavior modeled in the adults around them. Parents and other caregivers should remember that certain methods of discipline, particularly if harsh or shame provoking, can be detrimental to a child's self-esteem. Several different approaches to discipline have been adapted by various ethnic, cultural, religious, and socioeconomic groups. It is important to explore strategies with parents and caregivers; these methods are discussed in more detail in Chapter 50.

Talents and abilities should be recognized and highlighted. Children should know that their parents have confidence in their abilities and that any display of effort is appreciated. Even small successes should be noted and not overshadowed by either the large successes or the failures. Children thrive on the joy and pride they see in the eyes of their parents. Lack of encouragement can limit their optimism for continued success.

No parent wants his, her, or their child to feel badly about themselves. Indeed, from the perspective of most parents, self-esteem in itself is an important goal. Children with high self-esteem are happier, less likely to be depressed, and better able to persist in the face of challenges and failure. But high self-esteem is not achieved by withholding all criticism and praising without merit. In many ways, the importance of self-esteem lies in its role in the discussion of criticism and praise in careful parenting. Children need to feel good and confident about themselves while also perceiving themselves accurately and with self-awareness. There may be broad agreement about the goals, but neither is there a sole means of parenting nor a single prescription for how to talk with children. Pediatricians have a special role in bringing together all these elements as they advocate for the children under their care and the people those children are becoming.

CASE RESOLUTION

The health maintenance visit provides an opportunity for promoting parental support of the child's self-esteem. The pediatrician can interview the shy child and demonstrate the use of sincere general compliments to coax the child's engagement. The interviewer might invite her to speak about herself (eg, "What are your favorite things?" "What is your favorite color?"), while using humor and enthusiasm to engage her in sharing some details. This models interactions, which allows the child to demonstrate her autonomy, with the hope that this approach will be repeated by the parent at home. The health professional can reassure the girl and her mother that the child's overall health and development are normal. Additionally, after expressing appreciation for the careful, protective experience the parent has managed for the child, the physician should attempt to normalize the child's behavior for the parent. Although it may be important to directly discuss shyness in a developmental context, whether the girl is shy is not certain, and the parent's sense of deficiencies should be challenged by a view of developing competencies. Concrete suggestions should be offered for positive communication, such as minimizing "don't" and "no" phrases and being cognizant of how the parent speaks about the daughter. The parent should be encouraged to think about the child's temperament when considering involvement in multiple school activities but be reminded that the parent has not yet seen the child in an independent setting, where she may negotiate quite well and show sociability not yet evident at home.

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CHAPTER 47

Sibling Rivalry

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CASE STUDY

An 8-year-old boy is brought to the office for an annual checkup. During the course of the evaluation, his mother reports that her son and his 6-year-old sister are always fighting. She says her son hits his sister and pulls her hair, and nothing she does prevents them from fighting. The boy is a B student and has no behavior problems in school. The medical history and physical examination are completely normal.

Questions

1. What is sibling rivalry?
2. What is the physician's role in counseling a family about sibling rivalry?
3. What is the role of anticipatory guidance in preparing older children for the birth of a new sister or brother?
4. How does birth order and an individual's sex affect sibling rivalry?
5. What are some of the unique considerations related to sibling rivalry between stepsiblings?
6. What are some practical suggestions to share with parents about sibling rivalry?

Sibling relationships are important in helping children shape peer and, later, adult interactions. Moderate levels of sibling rivalry are a healthy indication that each child is assertive enough to express his or her needs or wants. Siblings educate and socialize together and mediate parental demands. Siblings often spend more time interacting with each other than with either parent. The sibling relationship is characterized by continuity and permanence, but the relationship is not without turmoil.

Sibling rivalry refers to the competitiveness between siblings based on the need for parental love and esteem. The rivalry is often characterized by jealousy, teasing, and bickering. The term was introduced in 1941 by David Levy, who described it as "a common feature of family life." Alfred Adler, the noted psychologist, described siblings as "striving for significance" within the family and noted that birth order had a strong influence on development. Historical examples of sibling rivalry include relationships between the biblical figures Cain and Abel, Joseph and his brothers, Jacob and Esau, and Leah and Rachel. Sibling rivalry is also noteworthy in pairs of celebrities, such as actresses Joan Fontaine (Academy Award winner for *Suspicion*) and her older sister, Olivia de Havilland (Academy Award winner for *To Each His Own* and *The Heiress*). Even after more than 40 years, the turbulence of their relationship has remained legendary, was termed one of the most dysfunctional sibling relationships in Hollywood, and may have had its roots in their simultaneous nomination for an Academy Award in 1942. By 1975, the sisters were no longer in communication with each other. Other siblings whose performances have often been compared include football players Peyton and Eli Manning, tennis stars Venus and Serena Williams, and musicians Liam and Noel Gallagher of Oasis and Ray and Dave Davies of the Kinks. Many Shakespearean plays have battling siblings. Television has included the issue of sibling rivalry in sitcoms, sometimes trivializing the challenges for parents. However, some shows portray unrealistic compatibility between children. Shows such as *Good Luck Charlie* and *Jessie* have shown large families in which conflicts are easily and humorously resolved. This may perpetuate unrealistic expectations in families. The 2019 comedy *Fighting With My Family* relates the true story of a former wrestler and the deterioration and subsequent competition that develops between a sister and brother and their careers as wrestlers.

Sibling rivalry is a universal phenomenon occurring even in the animal kingdom. For instance, the firstborn eaglet pushes the other eaglets out of the nest as soon as they are hatched as a way of ensuring an adequate food supply. Studies in animals show variation depending on brood or litter dominance and sex dominance (male or female) within the species. Aggressive interactions are more likely when there are multiple offspring in a single brood. Among wolves, however, older siblings help to feed and guard younger ones. In humans, the fear of displacement, dethronement, and loss of love occurs with the birth of a new brother or sister, leading to sibling rivalry. Older children fear they are not good enough and that their parents need to replace them with a new offspring. Such feelings lead to a fear of abandonment. Jealousy also plays a role, and older children may be angry with younger siblings for displacing them within the family.

Sibling rivalry frequently has a negative effect on parents because it is hard for them to see 1 of their children hurt, even if it is by a sister or a brother. The challenge for parents is to know when, and when not, to intervene and what strategies to use to minimize conflicts.

Physicians can help by offering anticipatory guidance to all parents and specific recommendations to parents who are experiencing such individual problems.

Sibling abuse is a relatively recent concept that recognizes the occurrence of physical, emotional, or sexual abuse of 1 sibling by another. The aggression may range from very mild to severe. Parents may not recognize the intensity of the aggression and may attribute negative interactions to sibling rivalry. Physicians should be knowledgeable about sibling abuse and be able to help parents to differentiate between rivalry and abuse.

Epidemiology

Sibling rivalry is a universal phenomenon, and a number of factors influence its development. Time interval between children affects the degree of rivalry, as does the age of the older children. Toddlers who are entering the "terrible 2s" may have a particularly hard time mastering independence and tolerating the presence of their younger sibling. Close spacing results in more problems, particularly when children are fewer than 2 years apart. In such situations, older children still have dependency needs, often feel less secure, and experience a need for maternal attention. They stay closer to mothers, are less playful, and are tenser. Closely spaced children engage in less spontaneous play, seem angrier, and issue sterner commands to their playmates. Sex of a new sibling also influences the relationship. There tends to be greater rivalry between same-sex siblings. Additionally, a child's temperament affects sibling relationships. The 3 components of temperament include emotional intensity, activity level, and sociability. It is also important to remember that children are egocentric, which, according to Erich Fromm, lasts through 8 years of age. This contributes to a child's willingness to share (including toys and parental attention) and to act unselfishly.

Position in the family also influences sibling rivalry. Middle children experience what is referred to as middle-child syndrome; they lack the prestige of older children and the privileges of younger ones. These children are often the least secure and strive hardest to gain affection. Special difficulties may develop if middle children are the same sex as older ones. Middle children grow up to be flexible, adaptable, and good negotiators. In myths and folklore, youngest children are "favorites." They are often the ones defended by parents when there are bouts of fighting.

Twins rarely present a problem of sibling rivalry; instead, they have a problem maintaining their individuality. However, sets of twins create problems for older siblings because the older siblings are not as unique as the pair of twins.

Stepsiblings also present a unique problem in sibling rivalry. Children of divorce frequently feel abandoned by 1 parent and in competition for the time and love of the custodial parent (see Chapter 149). Competition with stepsiblings is especially difficult if the stepsiblings are in the same home.

There are also unique considerations when 1 child has a chronic or potentially terminal illness or long-term disability. Similarly, being the sibling of a gifted child (see Chapter 35) places unique challenges on sibling relationships. The unique strengths of each child need to be acknowledged.

Issues of sibling conflict change over time. Toddlers are protective of their toys and belongings and are particularly upset when a younger sibling touches their possessions. Sharing is a challenging theme of the toddler years. During their school-age years children are concerned about equity and fairness. They may be upset by what they construe as preferential treatment (eg, when a 1-year-old sibling is not expected to put his or her toys away). Sibling competitiveness is said to peak between the ages of 10 and 15 years. Adolescents, with their additional responsibilities, including minding younger siblings, may resent the siblings for imposing on their time. Sibling rivalry can persist into adulthood, and one-third of adults describe their relationship with a sibling as distant or rivalrous. After age 60 years, 80% of siblings report being close.

Significant sibling abuse is said to affect 3 in 100 children. Less violent abuse is reported to occur in as many as 35 per 100 children. These figures are reported to cross all socioeconomic levels.

Clinical Presentation

Parental concerns related to sibling rivalry consist of fighting between siblings, including physical violence and verbal abuse, bickering, and regression to immature behavioral patterns. Although such immature behavior occurs most often following the birth of a new baby, it may also be apparent if 1 sibling is receiving more attention, such as during an illness or after a major accomplishment. Regressive behavior includes bed-wetting, drinking from a bottle, and wanting to be carried to bed. Substitution behavior, such as nail-biting in place of biting the new sibling, may occur after the birth of a new baby.

Before the birth of a new baby, parents may report that their children exhibit temper tantrums, irritability, and solemnness. They may mimic the pregnancy by eating a lot and putting a pillow under their clothes. In addition, children may have psychosomatic symptoms such as stomachaches or headaches. Risk factors for maladjustment following the addition of a sibling include family discord, physical or emotional exhaustion in parents, and housing insecurity. Conversely, a good marital relationship and family support facilitates the adjustment to new siblings.

Differential Diagnosis

Dilemmas concerning the correct diagnosis of sibling rivalry most often relate to the appearance of behavioral changes, such as regressive or aggressive patterns after the birth of a new sibling. For example, a child who was previously toilet trained may become incontinent of urine. Although urinary tract infection may be considered in the diagnosis, a careful history concerning the birth of the sibling reveals the correct etiology.

The other issue to consider is whether the sibling rivalry has moved into the arena of sibling abuse. Risk factors for sibling abuse include the absence of parents from the home, domestic or community violence, and children having inappropriate family roles (eg, having to care for younger siblings).

Evaluation

The evaluation of children with suspected sibling rivalry involves a history of the problem and parental strategies for addressing the difficulties. The parent should be particularly queried about 1-to-1 opportunities between parents and individual children. Physical examination and laboratory assessment are noncontributory.

If there is concern for sibling abuse, appropriate additional questions include the following: Is one child always avoiding another sibling? Has there been a significant change in a child's behavior? Does one sibling always seem to be the aggressor and the other the target?

Management

The focus of management is to allow parents to recognize the normalcy of sibling rivalry while helping them define the behaviors that are acceptable or unacceptable within the family context and to recognize when the rivalry has progressed to sibling abuse. Children fight more often in families when parents condone fighting and aggression between siblings as normal behavior. Likewise, children of parents who are angry may interact with their siblings through anger. Parents should be counseled about this. Parents may not appreciate their child's fear of loss of parental love as the basis of sibling conflicts. They should be reminded that many children think, "If I am so good, why do I have to be replaced?" Parents should be prompted to empathize by imagining how they would feel if their spouse brought home another mate, even if they were reassured about being loved. Physicians can also help parents address sibling rivalry by having them consider their treatment of children in terms of uniqueness versus uniformity and quality versus inequality. In general, parents should be advised to set the ground rules for acceptable behavior. Such rules include no hitting, punching, hairpulling, name-calling, cursing, or door slamming. There may be a neutral area in the home that can be set aside for arbitration should disagreements arise. Moving to a neutral area also allows for some time to cool off. Parents should be reminded that children who are hungry, tired, or bored are more easily frustrated and may start fights more readily.

Birth of New Siblings

Parents may notice behavioral changes in their children before the birth of a new sibling. These changes depend on the age of the children and presence of other siblings. Children should be told about the upcoming birth. The timing depends on the children's age; younger children do not need much lead time. Some studies have evaluated the inclusion of older children in the birthing process. The results of these studies vary, but they suggest that children younger than 4 years need their mother for emotional support and are concerned about her physical exertion during the birthing process. Some older children may also want to distance themselves from the actual events.

Physicians should suggest that older children be involved in planning for the arrival of the new baby as a means of minimizing their feelings of exclusion. For example, they can help purchase clothes or prepare the baby's room. Physicians should also suggest that parents purchase a gift for older children that represents a present from the new baby, such as T-shirts that announce the older sibling's new status, such as "big sister" or "big brother." In addition, older siblings may be given a doll to serve as a baby they can care for. Parents should point out the advantages of being older with comments such as, "You can stay up later," or "You can walk and play with all these toys." Frequently, the birth of a new baby is met with regressive behavior in older siblings. Regressive behavior should be addressed with tolerance and a realization that symptoms resolve with time.

Once the birth mother goes to the hospital, she should be advised to maintain contact with older children by telephoning or video chatting. Video chatting will also allow the older siblings to see the new addition to their family. Many hospitals now allow for visitation by siblings. Currently, hospital stays are so brief (often just 24 hours) that this period of separation is much shorter than it was previously. Household changes that may be necessitated by the birth of the new baby, such as room changes, the substitution of a bed for a crib, and entrance into nursery school, should be made before the arrival of the new baby.

Rivalry Between Older Children

Physicians need to consider individual parenting techniques when counseling parents of older children. Parents who compare 1 child with the other may foster contentious behavior, and those who strive to treat all children equally may inadvertently perpetuate rivalry. Children need to feel that they are unique rather than ordinary. For example, parents who buy both children the same presents may think they are preventing rivalry from developing, but they are actually depriving each child of a sense of uniqueness. The harder parents try to be uniform, the more vigilantly children may look for inequality. Each child needs a parent's undivided attention and time alone together. Siblings also need time apart from each other, and they should be encouraged to hold separate playdates and individual activities. Not all children in a family need piano lessons and soccer practice. Individuality and uniqueness are important. The more agreeable a parent-child relationship is, the more agreeable a sibling-sibling relationship is because each child has good self-esteem. Practitioners should recommend uniqueness and quality in each parent-child relationship.

Parents sometimes have to contend with sibling rivalry between older children. Physicians should reassure parents that these older children should be allowed to vent their negative feelings toward each other. For example, if a girl refers to her brother by saying, "I hate him," the parents should respond by validating these emotions and saying something like, "It sounds as if he's done something to really annoy you." Parents should also be advised not to take sides. They should examine how they usually respond to squabbling between siblings. Is one child's name always called first during a fight? Do they perpetuate sibling rivalry by using certain nicknames (eg, "turkey brain") or other derogatory terms? Parents should assume that both parties are at least partially guilty and should not allow themselves to be drawn into the fight as referees. Parents can respond to a request for arbitration with a statement such as, "I wasn't here when things started, so I don't know who is right or wrong." The parents should also advise siblings that they do not have to be friends with

one another, but they should not hurt each other's feelings. Positive, authoritative parenting should be encouraged (see Chapter 50).

Anticipatory guidance helps parents anticipate conflictual situations, such as who sits where during long car rides and who holds the remote control. Family meetings can be held to determine the ground rules that may avoid such battles. If conflicts arise, children should be allowed to work out a solution by themselves, with the stipulation that the parents will solve the problem if the children do not reach an agreement. If fights between siblings have recurrent themes (eg, which television shows to watch [who controls the remote] or video games to play), parents can devise a weekly schedule. Failure to abide by the schedule means both children forfeit the activity. If borrowing is the source of disputes, children who borrow from their siblings should leave collateral, which gets given back when the borrowed item is returned. Box 47.1 lists suggestions for parents who are seeking advice about fighting between children.

Siblings of Children With Special Health Care Needs

Nearly 1 in 5 children in the United States is a child with special health care needs (see Chapter 44). Caring for such children places increased demands on parents and their resources, and there is less parental attention or time available for unaffected siblings. Integrating the unaffected sibling into the families' care plan and activities can be empowering for children and positively influence their self-esteem. As with all children, time alone between unaffected children and parents should be strongly encouraged. Support groups for siblings of children with special health care needs have been demonstrated to help youngsters cope and deal with their often-conflicted feelings of anger at the special attention their brother or sister receives and their guilt about being healthy.

Box 47.1. Coping With Rivalry Between Siblings: Physicians' Advice to Parents

Dos

- Allow children to vent negative feelings.
- Encourage children to develop solutions.
- Anticipate problem situations.
- Foster individuality in each child.
- Spend time with children individually.
- Compliment children when they are playing together.
- Tell children about the conflicts you had with your siblings when you were children.
- Define acceptable and unacceptable behavior.

Don'ts

- Take sides.
- Serve as a referee.
- Foster rivalry.
- Use derogatory names.
- Permit physical or verbal abuse between siblings.

Sibling Abuse

Addressing sibling rivalry can reduce the risk of the rivalry progressing to abuse. As noted previously, setting ground rules, spending time with individual children, and modelling conflict-solving skills and nonviolent behavior are positive preventive measures.

If violence does occur between siblings, parents should separate the children immediately and clearly state that such behavior is unacceptable. Children should be given a cooling off period, and then parents should convene a family meeting. Parents should encourage children to discuss their feelings and devise solutions if similar situations arise in the future. If violent behavior continues, the family should be advised to seek professional family and mental health services.

Prognosis

Although sibling rivalry may last for years, most siblings become good friends as adults. Occasionally, mental health services are needed, especially if the sibling conflict has led to marital discord, there is concern about physical or severe emotional harm, or there is evidence of another psychiatric disorder, such as depression. Learning how to negotiate with one's siblings enables children to develop skills to collaborate with peers and colleagues as adolescents and adults.

CASE RESOLUTION

The mother should be advised not to serve as a referee. She should learn how to validate each child's feelings about the other. The physician can help her by talking to her son about his feelings. The mother should be advised to have a discussion with her children during which each child has the opportunity to define areas of conflict and the means to resolve them. The mother has the right and responsibility to prohibit physical fighting and encourage verbal dialogue.

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CHAPTER 48

Toilet Training

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CASE STUDY

A 2-year-old boy is brought to the office for a well-child visit. His mother, who is about to begin toilet training her son, asks your advice. The mother says that by the time her daughter was 2 years old she was already toilet trained, and she wants to know if training her son will be any different. The boy was the product of a full-term pregnancy and a normal delivery. He has been in good health, and his immunizations are current. He is developmentally normal, uses some 2-word phrases, and has been walking since the age of 13 months. His physical examination is normal.

Questions

1. When should the physician begin discussing toilet training with parents?
2. What factors help determine a child's readiness to begin toilet training?
3. Is toilet training in boys different from toilet training in girls?
4. What are some of the methods used to toilet train children?

The age at which toilet training is carried out is culturally determined. Some cultures train children at a very early age. For example, among the Digo, an East African tribe, some children between 2 and 3 months of age are conditioned to urinate or defecate when placed in certain positions. In the United States, the cultural emphasis is on the learning aspects of toilet training rather than the conditioning aspects. Training based on the learning aspects focuses on the cognitive development of children and children's readiness to learn the complexity of the task.

Toilet training is potentially a rewarding and frustrating experience for children and parents alike. Parents may have unrealistic expectations of their child's capability or may be quite intolerant of normal accidents that occur in the training process. It is important for the physician to introduce the topic of toilet training early on to prevent these unrealistic expectations. Refusal by a child to toilet train or accidents related to toilet training are often cited as a precipitating event for child physical abuse. It is recommended that the physician introduce to parents the issue of toilet training and provide anticipatory guidance by the time a child is 18 to 24 months of age to help parents develop reasonable expectations.

Epidemiology

The age at which children are toilet trained varies depending on social considerations and pressures. Before the 1920s, the approach to toilet training in the United States was permissive. After this attitude changed, the training methods became more rigorous, requiring that children be trained at an earlier age. In 1947, only 5% of children in the United States were not trained by 33 months of age, but by 1975 this figure had increased to 42%. Currently, approximately 25% of typically developing US children are daytime toilet trained at 24 months of age and 98% by 36 months of age.

The renewed interest in earlier toilet training in the United States has been attributed to 3 societal factors: the lower cost and increased options for child care and schooling associated with children after they are toilet trained, concerns about contagious illnesses (eg, hepatitis and infectious diarrhea in child care facilities in which diapers are changed), and the adverse environmental effects of nonbiodegradable disposable diapers.

Generally, girls are trained a bit earlier than boys, but only by a matter of a few months. Additionally, younger siblings often require less time to achieve daytime continence than firstborn children. Most children (80%) are trained simultaneously for bladder and bowel control. Approximately 12% are trained first for bowel control, with approximately 8% trained first for bladder control. Girls achieve nighttime continence at a younger age than boys.

Pathophysiology

Toilet training involves the ability to inhibit a normal reflex release action and then relax the inhibition of the involved muscles. For the process to be successful, a certain degree of neurologic and biological development is essential. Although a recent literature review found no consensus on which or how many readiness signs are ideal to start toilet training, several factors affect a child's toilet training readiness. Myelination of the pyramidal tracts and conditioned reflex sphincter control are necessary. Voluntary control is evidenced by myelination of the pyramidal tracts by age 12 to 18 months. Conditioned reflex sphincter control occurs by 9 months of age, and voluntary cooperation occurs between 12 and 15 months of age. In assessing the neurologic development of children, walking is viewed as 1 of the milestones that indicate motor readiness for toilet training. Appropriate motor skills, including getting to the bathroom, being able to remove clothing,

and sitting on the toilet, are also key skills required for successful toilet training.

Toilet training depends on physiologic and psychological readiness. Cognitive development is assessed by a child's ability to follow certain instructions and understand what the potty is used for. Two years of age has been suggested as the appropriate age to initiate toilet training in most children given that the developmental and physiologic skills necessary for successful toilet training begin maturing at this time. Toilet training usually takes 2 weeks to 2 months to master. Achieving nighttime continence is often separate from daytime continence. Although opinions about nighttime wetting are culturally dependent, it is considered normal in the United States up to 6 years of age.

A child's temperament can also affect the success of toilet training. Children who struggle with inflexibility, are less persistent, or have a more negative mood often experience delays in toilet training. Unlike physiologic or psychological readiness, temperament is not likely to change after a 2-month delay in training; understanding a child's temperament can better assist parents in supporting their child through the process of toilet training. In addition to the child's temperament, the child's emotional readiness is influenced by parental attitudes and parent-child interactions.

Differential Diagnosis

The differential diagnosis of toilet training difficulties focuses on factors that contribute to a delay in acquisition of skills. The physician should look for associated symptoms, such as dysuria, a weak urinary stream, constantly wet underwear, or fecal soiling when assessing a child who continues to manifest signs of urinary or stool incontinence. Additionally, it is important to determine if children are essentially toilet trained but are having intermittent accidents.

Dysfunctional voiding involves an abnormal voiding pattern stemming from a problem with the bladder filling or emptying. Such voiding is characterized by urine leakage, an increase in urgency, and an increase in frequency, and it often results in frequent urinary tract infections (UTIs). The most common cause of isolated daytime wetting in previously trained children is UTI (see Chapter 112). Although UTI is not associated with age at the onset of toilet training, earlier toilet training is associated with later onset of UTIs. No association exists between toilet training methods and dysfunctional voiding. Chemical urethritis may also be associated with urinary incontinence. Stress incontinence, which has also been called "giggle incontinence," may result in wetting. *Urgency incontinence* occurs when children delay going to the bathroom and then are unable to hold urine any longer. Some children have ectopic ureters, which can empty into the lower portion of the bladder, vagina, or urethra and cause a constant dribble of urine. Labial fusion with vaginal reflux of urine may also be associated with daytime wetting. Urine pools behind the fused labia or labia that do not separate sufficiently to allow natural egress during voiding, and when the child stands up the urine exits. The child with a neurogenic bladder may also have symptoms of daytime enuresis.

Stool-related accidents may be associated with chronic constipation and overflow incontinence or with congenital megacolon (ie, Hirschsprung disease; see Chapter 56). Stool toileting refusal occurs when a child is trained to urinate in the toilet but refuses to defecate in the toilet for at least 1 month. Although many parents perceive stool toileting refusal as insignificant, it is often associated with developing encopresis, constipation, painful bowel movements, and delayed completion of toilet training. If a child has persistent constipation, the child may develop megacolon and may not be able to sense a full rectum, thereby causing overflow of loose stools. A complete history and physical examination are required to differentiate functional constipation from organic causes. The physician should recognize and address functional constipation early to avoid acquired megacolon, because it takes 3 to 12 months to treat megacolon caused by chronic constipation. Children who prefer to stand in a corner to defecate should be commended for recognizing their physiologic urge. However, parents should be aware that children who hide while passing stool in their diaper are more likely to exhibit stool toileting refusal and be constipated. Successful management of constipation may decrease the incidence of toileting refusal.

Evaluation

History

Typically developing toddlers should be assessed for their physiologic and psychological readiness to initiate toilet training, as well as for any underlying medical conditions that may affect their ability to learn toileting skills at the customary age. The physician should provide anticipatory guidance to parents about toileting readiness. Affirmative answers should be obtained to the following 3 questions:

1. Does the child exhibit bladder control as evidenced by periods of dryness that last up to 2 hours and facial expressions that show the child's physiologic response to the elimination process?
2. Does the child have the motor skills necessary to get around? This essentially involves the child's ability to walk and remove their clothing.
3. Does the child have the cognitive ability to understand the task at hand?

Cognitive ability can be assessed by giving a child 10 one-step tasks to determine whether the child can complete at least 8 of the 10 tasks (Box 48.1). The ability to carry out these tasks does not ensure a willingness to be toilet trained, however. When language readiness is apparent (ie, use of 2-word phrases and 2-step commands), training can commence. In addition to language readiness, understanding of the cause and effect of toileting, desiring independence, and having sufficient motor skills and body awareness are helpful for successful training.

Stress in the home may negatively affect a toddler's ability to master the task of toilet training. The physician might counsel a family to delay toilet training if the family has moved recently, the birth of a new baby is expected, or a major family crisis has occurred, such as a death or serious illness.

The child who has had difficulties with toilet training must undergo a similar assessment.

Box 48.1. Requests or Imperatives Used to Help Assess Toilet Training Readiness

- Bring me the ball.
- Go to the door.
- Sit on the chair.
- Pick up the doll.
- Open the door.
- Give the pen to your mom.
- Put the ball on the table.
- Put the doll on the floor.
- Take off your shoes.
- Open the book.

Physical Examination

A physical examination should be performed to rule out underlying problems, such as spina bifida occulta, which may be associated with a neurogenic bladder. A neurologic examination may reveal nerve damage impeding muscles from relaxing or tightening at the right time. A careful examination of the genitalia is important in the child with urinary incontinence to determine if conditions such as labial fusion, meatal stenosis, or posterior urethral valves are evident. In the child with a problem related to passage of stool, the physician should check for an abdomen with feces-filled intestines, which is a sign of obstipation. Additionally, a rectal examination should be considered to determine the presence of hard or impacted stools or any other abnormalities in the anal area.

Laboratory Tests

Although a laboratory assessment is not indicated in the normal toddler who is being toilet trained, diagnostic studies may be appropriate in the child who is having problems with training. In the older child, urinalysis may show evidence of a UTI.

Management

The physician should help parents understand the appropriate approach to the toilet training process. Unfortunately, most parents do not obtain the necessary advice from physicians. In 1 report, no parents attending a clinic and only 7% of parents in a private practice received advice about toilet training from their physician. Therefore, it is important for the physician to initiate the discussion early enough to prevent the development of any problems.

Two main contrasting styles of toilet training exist. The first method, which is endorsed by the American Academy of Pediatrics (AAP), is a child-oriented approach that stresses the child's physiologic and psychological readiness to toilet train. The 3 versions of this approach are the Brazelton method, the AAP guidelines, and the Dr. Spock method, all of which use the same components with only minor variations. All involve gradual training and emphasize the use of rewards rather than punishments.

When toilet training the typically developing child, a parent should be advised to take the approach outlined in Box 48.2.

Additional suggestions involve allowing children to have their undergarments off and keeping the potty chair near them during play.

Children who use the potty successfully should be rewarded. Rewards can be in the form of verbal comments such as "Mommy is so proud of you," hand clapping, or the use of star charts that can be redeemed for rewards. Children can be consulted about what rewards they like. The AAP recommends using praise rather than treats for reinforcement. Punishment should not be used, particularly physical punishment. One report indicates that 15% of parents of clinic patients believe that spanking their children for accidents is acceptable. Parental disapproval of accidents can be articulated; however, parents should understand that accidents may continue to occur for months. *Regression*, that is, the state of being no longer willing or able to execute toilet training skills, may also occur with stressors, such as a recent move, a new sibling, or divorce. Consistent parental reminders and a consistent schedule can assist with eliminating regression. It is important to normalize regression and encourage parents to focus on regression as a temporary step on the way to being successfully toilet trained.

The second method, described by Azrin and Foxx, is parent-oriented and uses intense operant conditioning methods and a potty doll to assist with learning. The 6 components of the method include increasing the amount of fluids consumed; regularly scheduled times for toileting, starting with 15-minute intervals; positive reinforcement for asking about, approaching, or sitting on the potty chair; lowering/raising pants and successful urination or defecation in the potty chair; time-out from positive reinforcement/cleanliness training following accidents; and teaching the child to differentiate between wet and dry pants, checking for dry pants every 5 minutes. Although this method has been effective in training children, including those individuals with intellectual disabilities, it is not recommended for training typically developing children. A child with autism spectrum disorder who does not understand the social reward system recommended by the AAP may benefit from the intense conditioning methods described by Azrin and Foxx.

Two additional conditioning methods are available that are less commonly used in North America. The first is assisted newborn toilet training, which begins when the newborn is 2 to 3 weeks of age. The baby is placed over a toilet after feeding or if showing signs of elimination and is rewarded with food or affection for voiding or passing stool. The second method focuses on elimination communication and begins at birth. The parent learns baby's body language, noises, and elimination patterns. The parent also makes noises, such as the sound of running water, to associate with voiding while the newborn is placed in positions to facilitate elimination. Interest in these conditioning methods has increased in the past few years.

A child may use training pants, which are thickened underwear, or disposable diaper-like underwear, rather than diapers. Standard

Box 48.2. Toilet Training Approach for the Typically Developing Child

1. Teach children the appropriate vocabulary related to the toilet training process. This could include words such as "pee," "poop," "urine," "stool," "dry," "wet," "clean," "messy," and "potty."
2. Tell children what the purpose of the potty is. Placing the contents of a soiled diaper into the toilet can educate them on the purpose of the potty. Generally, a child potty chair should be purchased. The potty chair has several advantages over the toilet. Parents can encourage children to decorate the potty and put their names on it. The potty can be kept in a place where children spend much of their time, not necessarily in the bathroom. Children can sit on the potty and have their feet on the floor, which is more physiologically sound and gives them a greater sense of security. Parents should suggest that children stand fully clothed in the bathroom as an initial step in encouraging their use of a potty. Children should be allowed to sit on the potty with their clothes on for approximately 1 week before the process of toilet training begins. Next, children should sit on the potty without their undergarments, but no attempt should be made to catch stool or urine. Boys should learn to urinate in the seated position, because they may otherwise resist sitting for defecation.

   When away from home, the potty chair should be packed to maintain the established routine. It is important that all individuals caring for the child (eg, grandparents, babysitters) understand the parent's or parents' plans for toilet training.

   Toilet adapter rings can be used if the family is resistant to using a potty chair or if the transition from a potty chair to the toilet is likely to be stressful, as is true for many children with autism spectrum disorder. Adapter rings fit directly onto the toilet and do not require emptying, as do separate potty chairs. They require that the toddler climb up on the toilet, and they need to be removed for others to use the toilet. A step stool should be used to aid in climbing onto the toilet and to provide more leverage while defecating.
3. Encourage cleanliness and dryness by changing children frequently. Parents should ask their children whether they need to be changed using the appropriate vocabulary. This phase is important to continue as the toilet training process proceeds. Some parents mistakenly do not change their soiled children as a means of punishing them for having accidents. This gives children a confusing message about the need for cleanliness.
4. Explain to children the connection between dry pants and going to the potty. Children should understand that dry pants feel good and that they can keep their pants dry by going to the potty.
5. Help children understand the physiologic signals for using the toilet. Parents can facilitate this by observing children's behavior around the time of elimination and making comments such as, "When you jump up and down like that, Mommy knows you have to go to the bathroom."
6. Children must have the physiologic ability to postpone the "urge to go." This usually occurs when children are capable of delaying voiding for at least 2 hours. Parents then can initiate toilet training by taking children to the bathroom at 2-hour intervals. Additionally, children should sit on the toilet immediately after naps and 20 minutes after meals. Children should not be left on the toilet for more than 5 minutes and should be permitted to get up if they want. While sitting on the potty, they can be entertained with reading a story or playing games. It is helpful to have designated toys or books enjoyed only when the child is sitting on the potty. Parents are encouraged to rotate the toys so toilet training continues to be interesting to the child.

underwear is promoted as advantageous because it feels different from diapers and encourages the use of the potty. Using a bigger size or snipping the waistband facilitates children's ability to remove their underpants and can be recommended.

Some children seem fearful of certain aspects of the toilet training process, including fear of falling into the toilet, which can be circumvented with the use of a potty or toilet adapter rings, and fear of the noise of the flush. Allowing a child to flush the toilet without using it may dispel the fear. Toilet phobias can cause children to hold their urine until the last moment, resulting in wetting, or cause children to hurry and not fully empty their bladder, resulting in possible infections. Some children become fascinated with flushing or unrolling toilet paper, and parents should discourage children from wasting water or paper.

Modeling is 1 of the major components of toilet training children. Children should be allowed to enter the bathroom with parents and even sit on the potty chair as a parent sits on the toilet. Some children who are quite strong-willed and independent, coupled with perfectionist parents, may have problems with toilet training.

Special considerations must be made for children attending child care. Children should have open bathroom privileges; that is, they should be permitted to leave the room to go to the bathroom without raising their hands or receiving other reminders. Child care offers the advantage of peer modeling and peer pressure during the toilet training process. Potty chairs should not be used in child care settings because of the risk of infectious diseases.

Children with special needs generally encounter more obstacles when mastering toileting. Communication delays, less developed motor skills, sensitivity to stimulation, and preference for routine are just a few of the additional challenges that make it difficult to ascertain whether the child is ready to toilet train. Although incontinence was once thought to be inevitable for children with special needs, it is important for parents to understand that continence can be achieved but that expectations need to modified (ie, it may take until age 5 years to achieve, and standard toilet training methods rarely are successful).

Medications have a limited role in toilet training. Although some physicians recommend the use of drugs to increase bladder capacity, such drugs should not be used because they do not assist children with the toilet training process. However, children who are constipated may require stool softeners, such as mineral oil, polyethylene glycol solution, or magnesium citrate, or the addition of fiber bulk to their diet as well as increased fluid consumption to facilitate the passing of stool. The child who seems to have particularly challenging

toilet training problems should be seen by the physician on a weekly or biweekly basis until the child exhibits improvement.

Parents can also be referred to the many books on toilet training, particularly if problems arise. Many books are written for children to help them understand their body and the elimination process. Videos are also available to help children with toilet training. A child may benefit from the opportunity to practice with dolls designed to wet or poop after being fed.

Prevention

If a child demonstrates resistance to toilet training, the process should be delayed for 1 to 2 months. The child who learns how to withhold needs additional time to learn how to relax the sphincter when sitting on a potty. It is important for parents to avoid an aggressiveness/resistance struggle, because this may become the source of future bowel problems, including constipation. The child who is regular, particularly the individual who has a bowel movement at the same time every day, is more easily toilet trained. Creating a regularly scheduled toilet sitting session can assist with reducing the incidence of or stopping withholding.

Prognosis

All typically developing children are eventually toilet trained. The age at which this occurs varies and is significant only if it restricts a child from participating in school.

CASE RESOLUTION

The mother in the case history should be advised that this is a good time to initiate the toilet training process. She should be told that boys, as a group, are successfully toilet trained at a later age than girls. Her son can be assessed to determine whether he can follow at least 8 of 10 instructions (Box 48.1). If the boy can do so, the mother should be given the stepwise approach to initiating the toilet training process. The mother should be informed it may take months to years to achieve nighttime continence after daytime continence is achieved.

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CHAPTER 49

Crying and Colic

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CASE STUDY

The parents of a 2-week-old neonate bring their son to the emergency department because he has been crying persistently for the past 4 hours. He has no history of fever, vomiting, diarrhea, upper respiratory tract infection, or change in feeding. The newborn is breastfed.

On physical examination, the neonate appears well developed and well nourished. His weight is 3.37 kg (7.4 lb), which is 0.20 kg (0.4 lb) more than when he was born. Although he is fussy and crying, he is afebrile with normal vital signs. The remainder of the physical examination is within normal limits.

Questions

1. What is the normal crying pattern in newborns and young infants?
2. What is colic?
3. What conditions are associated with prolonged crying in newborns and young infants?
4. What are key factors in the history of crying newborns and infants?
5. What tests or studies, if any, are indicated in crying newborns and infants?
6. What are a few of the management strategies that can be used by parents to soothe their crying or colicky newborns and infants?

Crying is an important method of communication between babies and caregivers; it is nonspecific, however, and many stimuli (eg, hunger, fatigue, pain) can provoke the same response. Parents report that they can discriminate among various types of cries in their babies. Crying can be divided into 3 categories: normal or physiologic crying, excessive crying secondary to distress (eg, hunger) or disease, and excessive crying without an apparent cause (eg, colic).

The difference between normal and excessive crying may be more qualitative than quantitative. Some investigators have used the mnemonic "PURPLE" to characterize crying during early infancy focusing on the qualities that make the crying particularly frustrating to caregivers: P, peak pattern (increases weekly until 2 months of age); U, unexpected bouts of crying; R, resistance to soothing measures; P, pain-like facial grimacing; L, long periods of crying; and E, evening clustering. Deciding whether crying is excessive varies based on parental expectations and thresholds. Expressed parental concern about extreme crying or fussiness requires attention. If parents complain that newborns and infants cry inconsolably or continuously as well as excessively, the crying may have an underlying organic etiology. Crying with no organic etiology or definable cause is often attributed to colic.

Colic is a poorly understood, benign, self-limited condition in which healthy infants experience paroxysms of inconsolable crying. It manifests as unexplained crying in newborns and infants that usually occurs in the late afternoon or evening. During an episode of colic, babies cry and may draw the knees up to the chest or rigidly stiffen the legs, flex the elbows, clench the fists, and turn red (Figure 49.1). Although neonates and infants may appear to be miserable during an episode of colic, they are otherwise healthy, eat well, and demonstrate good weight gain.

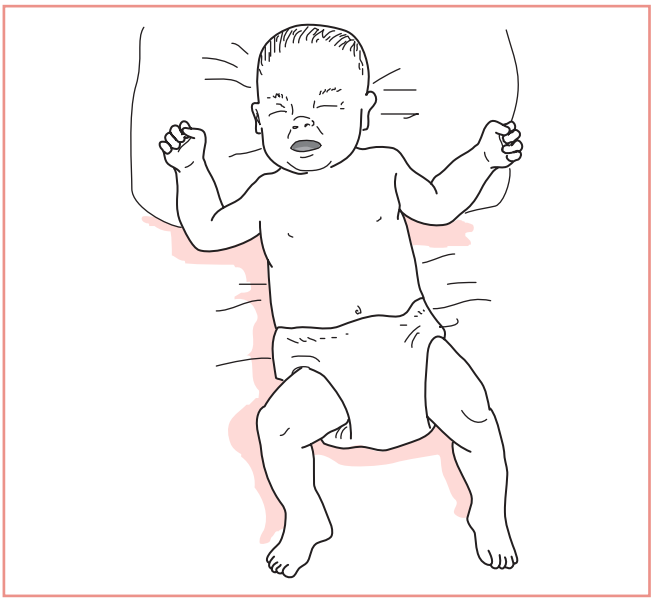

Figure 49.1. Illustration of a baby exhibiting characteristic physical signs of colic, such as crying, flexed elbows, and clenched fists.

Epidemiology

Qualitatively, *excessive crying* is any amount of crying that concerns or worries parents. Quantitatively, definitions of excessive crying have been based on the results of Brazelton's study of normal newborns

and infants. Excessive crying begins at 2 weeks of age (median daily crying time, approximately 2 hours per day), peaks at 6 weeks of age (median daily crying time, approximately 3 hours per day), and decreases to less than 1 hour per day by 12 weeks of age. More crying occurs during the evening hours, especially between ages 3 and 6 weeks.

Although many neonates and infants exhibit a relatively similar pattern of fussiness that peaks at approximately 6 weeks of age, those with colic tend to be inconsolable for longer periods and cry with greater intensity. Colic affects 10% to 20% of newborns and infants younger than 3 months. Colic affects both males and females equally and has no correlation with gestational age (eg, full-term vs preterm), type of feeding (eg, breast vs bottle), socioeconomic status, or season. Postpartum depression and abusive head trauma have been associated with colic and the stressfulness of infant crying. Colic usually begins at 2 to 3 weeks of age, peaks at 6 to 8 weeks of age, and resolves by 3 to 4 months of age. In general, symptoms of colic last for more than 3 hours per day, for more than 3 days per week, and for more than 3 weeks' duration (ie, *rule of 3s*).

Clinical Presentation

Colicky babies are otherwise healthy newborns and infants younger than 3 months who cry or fuss inconsolably for extended periods, usually during the afternoon or evening. Typically, the crying resolves within a few hours.

Pathophysiology

Crying is a complex vocalization that changes during the first year after birth as babies develop. In the first few weeks after birth, crying is a signal that newborns are experiencing a disturbance in homeostatic regulation (eg, hunger, discomfort). As babies mature and begin to differentiate internal from external stimuli, crying may also be an indication of too little or too much environmental stimulation. During the second half of the first year, as infants mature neurologically and gain voluntary control over vocalizations, crying can be an expression of different affects (eg, frustration, fear).

Various explanations for the etiology of colic have been proposed, but the cause remains unknown. Some authorities believe that colic may not be a pathologic entity but instead may be simply an extreme variant of normal crying. Proposed causes of colic include cow's milk protein or lactose intolerance, abnormal intestinal peristalsis, alterations in fecal microflora, gastrointestinal immaturity resulting in incomplete absorption of carbohydrates and resultant excessive gas production, increased serotonin secretion, poor feeding technique, and maternal smoking or nicotine replacement therapy. Recent studies have demonstrated increased levels of fecal calprotectin, a marker of colonic inflammation, in infants with colic. Others have proposed that colic is caused by problems in the interaction between babies and their environment, specifically their parents. This interactional theory requires not only excessive crying on the part of the newborn or infant but also an inability of the parents to soothe the crying baby. More than 1 of these factors may contribute to the pathogenesis of colic.

Differential Diagnosis

An acute episode of excessive crying may be secondary to disease (eg, fever, otitis media). An organic etiology should be suspected in newborns and infants who present with inconsolable crying of acute onset. Box 49.1 lists the most common causes of acute, unexplained, excessive crying in newborns and infants. Some conditions

Box 49.1. Common Causes of Acute, Unexplained, Excessive Crying in Newborns and Infants

Idiopathic[a]
- Colic[a]

Infectious
- Otitis media
- Urinary tract infection
- Stomatitis
- Meningitis

Gastrointestinal[a]
- Constipation
- Anal fissure
- Gaseous distention
- Peristalsis problems
- Reflux
- Pyloric stenosis
- Intussusception

Trauma
- Corneal abrasion
- Foreign body in the eye
- Hair tourniquet syndrome

Behavioral[a]
- Overstimulation
- Persistent night awakening

Drug Reactions
- Immunization reactions (previously common with diphtheria-tetanus-pertussis vaccine)
- Neonatal drug withdrawal (eg, narcotics)

Child Abuse
- Long bone fracture
- Retinal hemorrhage
- Intracranial hemorrhage

Hematologic[a]
- Sickle cell crisis

Genitourinary
- Incarcerated hernia
- Testicular torsion

Cardiovascular
- Arrhythmia (eg, supraventricular tachycardia)
- Congestive heart failure
- Anomalous left coronary artery[a]

[a] May present as acute or recurrent episodes of excessive crying.

occur in a more chronic or recurrent pattern, particularly if the condition is not treated.

The differential diagnosis of newborns and infants who experience recurrent episodes of excessive crying or recurrent night awakening associated with crying is focused more on behavior and temperament. Colic, neonatal abstinence syndrome, or difficult temperament (eg, extreme fussiness) may cause recurrent crying. Recurrent night awakening and difficult temperament are discussed in Chapters 30 and 51, respectively.

Evaluation

A thorough patient history and physical examination usually provide clues to the diagnosis in instances of acute onset of crying.

History

The focus of the history should be on determining the presence of any associated symptoms. Additionally, circumstances surrounding the crying (eg, occurrence during day or night) should be ascertained (Box 49.2).

Physical Examination

A thorough physical examination is required for accurate diagnosis. Red flags in the evaluation of crying infants include fever, lethargy, and abdominal tenderness or tenseness. The following aspects of the examination warrant particular attention:

1. Careful inspection of the skin after all clothing has been removed to look for any suspicious bruises or marks
2. Palpation of all long bones to detect occult fractures
3. Examination of all digits and the penis to check for hair tourniquets (ie, single strands of hair wrapped around digits or the penis)
4. Examination of the retina for retinal hemorrhages, which may be indicative of prior head injury
5. Eversion of the eyelids to check for ocular foreign bodies
6. Fluorescein staining of the cornea to look for corneal abrasion.

Laboratory Tests

With the exception of urinalysis, most screening laboratory tests likely are not useful unless indicated by the patient history and physical examination. Afebrile infants with urinary tract infection may present with crying. Even when the initial history and physical examination are nondiagnostic, a serious underlying condition (eg, intracranial hemorrhage, drug ingestion) should be suspected in babies who persist in crying inconsolably. Such newborns and infants may warrant an extended period of observation or a more extensive workup that includes laboratory assessment.

Imaging Studies

Radiographic studies may be necessary in some situations (eg, long bone radiographs for newborns and infants with long bone tenderness on palpation, cases of suspected child abuse). Computed tomography of the head should be performed on infants with retinal hemorrhage.

Management

Management of excessive crying is determined based on identification of the cause. Underlying organic conditions (eg, urinary tract infection, fractures) should be managed. The cornerstone of management of colic is parental reassurance and support, practical suggestions of feeding and handling techniques (eg, cuddling, holding), and education about the benign, self-limited nature of colic.

If symptoms persist and parents desire additional management, further treatment is individualized based on patient history, physical examination, and family characteristics. Common management techniques are listed in Box 49.3. First-line interventions that may be considered include changes in feeding techniques and/or soothing techniques, both of which address some of the potential etiologies of colic, including swallowed air and overstimulation. Currently, data on probiotic supplementation, dietary changes, various medications, and complementary and alternative medical therapies are insufficient for routine recommendation; however, such options may be considered on an individual basis after a discussion of the potential risks and benefits. Changes in sensory input (eg, soothing sounds or motions) may resolve crying and soothe colicky babies. Soothing techniques include using a pacifier, swaddling, shushing, swinging, rocking, rubbing the abdomen, holding the infant or placing the infant in a front carrier, providing white noise, and giving a warm

Box 49.2. What to Ask

The Newborn or Infant With Crying or Colic

- Is this the first time the newborn/infant has cried inconsolably, or does this happen on a recurring basis?
- Has the newborn/infant had a fever?
- Does the newborn/infant have any cold symptoms, vomiting, or diarrhea?
- Is the newborn/infant having any difficulty feeding? Is the newborn/infant formula-fed or breastfed?
- Has the newborn/infant had a recent fall or accident?
- What do you do when your newborn/infant cries?

Box 49.3. Management of Colic

- Parental reassurance
- Parental education
- Alteration in techniques of newborn/infant feeding and handling
  - Increased carrying
  - Responding quickly to crying
- Alteration of sensory input to the newborn/infant
- Prevention of swallowed air from passing through the pylorus
- Probiotics
- Dietary modifications
- Medication
- Complementary and alternative medicine therapies (after discussion of potential risks and benefits)

bath. Parents should be encouraged to experiment with various techniques, because the success of any given method may vary from 1 episode of colic to the next. Changes in feeding techniques to minimize the passage of swallowed air through the pylorus also can be useful. Such techniques include feeding in an upright position and limiting the period of sucking at the breast or bottle to approximately 10 minutes, after which time greater amounts of air are swallowed relative to the amount of milk or formula ingested. Some newborns and infants eat very fast and swallow a lot of air. Burping these babies every 5 to 10 minutes during feeds may help alleviate discomfort caused by excessive air swallowing (ie, aerophagia). Decreasing the size of the opening of a nipple for a bottle-fed baby may reduce the amount of air swallowing.

Data from several recent clinical trials indicate that in breastfed infants, use of the probiotic *Lactobacillus reuteri* DSM 17938 may decrease the duration of crying. A similar decrease in crying time has not been demonstrated in formula-fed infants given *L reuteri*.

Data on dietary changes, such as the use of hypoallergenic diets by breastfeeding mothers, are inconclusive but suggest that such changes may have some therapeutic benefits. Similarly, the use of partially, extensively, or completely hydrolyzed infant formulas also seems to have beneficial effects on the symptoms of colic. The switch to soy-based formulas is generally not recommended because soy can be an allergen. Generally, these dietary modifications should be reserved for newborns and infants with additional symptoms of allergy (eg, wheezing, rash) or intolerance (eg, vomiting, diarrhea, hematochezia, weight loss).

Various medications, including anticholinergic agents, motility-enhancing agents, proton-pump inhibitors, barbiturates, laxatives, and antiflatulence agents, have limited success and are best avoided. Currently, antiflatulence agents (eg, simethicone) are prescribed most commonly. Despite lack of scientific evidence to support their efficacy, anecdotal reports from parents indicate that they are effective.

Complementary and alternative medical therapies may be considered. Limited amounts (eg, 1–2 oz per day) of herbal remedies (eg, chamomile tea) can be administered if parents report satisfaction and no evidence exists of adverse effects. Evidence is insufficient to support the recommendation of physical therapies such as chiropractic or osteopathic manipulation, infant massage, or acupuncture. However, they may be considered on an individual basis after a discussion of the potential risks and benefits with the parents. Finally, physicians should encourage parents to respond to their baby's cries quickly and carry the baby as much as possible (eg, at least 3–4 hours per day). Parents should be advised that it is not possible to "spoil" babies younger than 4 months and that the baby's behavior may improve with increased parental responsiveness.

Prognosis

The physician should understand and should reassure the parent or parents that the natural history of persistent crying during infancy is one of resolution over time. Mothers of colicky newborns and infants have an increased likelihood of stopping breastfeeding early and also are at increased risk for postpartum depression. Excessively fussy babies are at increased risk for child abuse.

CASE RESOLUTION

The newborn is experiencing an acute episode of unexplained crying. Despite a normal physical examination, he was observed for 1 hour in the emergency department because his crying persisted. A septic workup was done, which resulted in the diagnosis of a urinary tract infection.

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CHAPTER 50

Discipline

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CASE STUDY

A 3-year-old boy is being threatened with expulsion from preschool because he is biting the other children. His mother states that he is very active and aggressive toward other children. In addition, his language development is delayed. She is at her wits' end about what to do. The birth history is normal, and the mother denies the use of drugs or cigarettes, but she drank socially before she realized she was pregnant. The medical and family histories are noncontributory, and the physical examination is normal.

Questions

1. What is the definition of discipline?
2. What are the 3 key components of discipline?
3. What is meant by parental monitoring?
4. What are 4 different parenting styles?
5. What strategies can parents use to discipline children?
6. What are the guidelines for using time-out?
7. What is the relationship between corporal punishment and child abuse?

Discipline can be defined as an educational process in which children learn how to behave in a socially acceptable manner. The word is derived from *disciplinare,* meaning to teach or instruct. It involves a complex set of interactions of attitudes, models, instructions, rewards, and punishments. Discipline is not synonymous with *punishment,* which denotes a negative consequence to one's actions. The goal of effective discipline is to help children gain self-control and respect for others and to learn behavior that is appropriate for given situations. It also serves to ensure a child's safety in the environment. *Proactive discipline* is action taken by parents to encourage good behavior, and *reactive discipline* is parental action following misbehavior. To be effective, child discipline must have 3 components: a learning environment with a positive, supportive parent-child relationship; a refined strategy for teaching and reinforcing desired behaviors; and a defined strategy for decreasing or extinguishing undesired behaviors. Children thrive in a supportive environment in which they are praised for socially appropriate behavior and are able to participate in the responsibilities and activities of the household. Appropriate discipline teaches a child empathy and to consider how other children feel when they are hit or teased. Parents, however, may be more focused on eliminating unwanted behaviors and may bring these specific concerns to their child's pediatrician.

Parental monitoring relates to the oversight of children's activities at home, in school, and in the community. The extent and form of parental monitoring varies with the age of the child. Parental monitoring occurs when parents ask their children, "With whom are you going to be? Where are you going? What will you be doing?" Parental oversight involves children's access to and use of the internet and social media (see Chapter 7). Inadequate parental monitoring has long-term sequelae, including an increased incidence of risk-related behaviors. Parental monitoring must be coupled with parental discipline to promote desirable behaviors and eliminate undesirable ones.

Anticipatory Guidance: Talking With Parents About Discipline

Practitioners can assist parents by giving them guidance about appropriate childhood discipline related to routine and problem development and to counsel about the scope of monitoring. The age and temperament of the child are important factors to consider. In addition, pediatricians can educate parents about corporal punishment, especially as the major method of discipline. Pediatricians also have a role in advising against corporal punishment in schools. While most states have banned corporal punishment in the school setting, 19 states, mostly in the south, still permit it.

Parenting Styles

Diana Baumrind is credited with delineating a classification of parenting styles, which are known as Baumrind's parenting typology and consist of 4 distinct categories. *Authoritarian* parenting focuses on specific rules and the belief that the rules should be followed without exception. Children are not encouraged to participate in decision-making or problem-solving. Children are punished for their mistakes and, as a consequence, self-esteem may be negatively affected.

Authoritative parenting, however, encourages participation of children in decision-making and focuses on positive discipline strategies and reinforcing desired behaviors. Rules and consequences do exist, but children play a participatory role. Children's feelings are considered, children learn empathy, and high self-esteem is fostered.

Permissive parenting is also referred to as indulgent or lenient parenting. Rules are rarely enforced, although children may be

threatened, such as, "If you do that again, you will be grounded. I really mean it this time!" Children may feel anxious because they are uncertain about the boundaries that might separate them from harmful decisions they make on their own.

Uninvolved parenting occurs when parents may be more involved in their own lives and have less interest in or time with their children. They are unaware of their children's progress in school, their children's interests, or their children's friends.

These categories suggest mutually exclusive parenting styles, but many parents use all styles for truly effective parenting. There are times when parents may have to say, "Because I said so" (authoritarian), and other times when they say, "Go ahead; it's fine with me if you want to try that" (permissive).

Regardless of parenting style, it is important to encourage parents to establish a positive interactive environment with verbal communication, monitoring children's behavior and commending desirable behavior, ignoring trivial problems, and consistently applying predetermined consequences for misbehavior. Psychologist Marshall B. Rosenberg promotes the concept of *compassionate communication,* using the analogy of the language of the giraffe, which is a language of requests, versus the language of the jackal, one of demands. Identifying feelings is integral to the language of giraffes. Rules should be simple, clear, and established ahead of time.

Frequently, physicians fail to inquire about children's behavior. Unless parents bring up the topic, discipline is not routinely discussed during the physician visit. On average, physicians spend only 90 seconds per visit on anticipatory guidance and counseling. However, a survey of mothers in a physician waiting room showed that up to 90% were concerned about 1 aspect of behavior. Sixty percent of mothers surveyed found physician advice quite helpful. The American Academy of Pediatrics recommends anticipatory guidance about discipline at each health supervision visit between 9 months and 5 years, and studies report that physicians counsel parents about discipline about 40% of the time. Such counseling is especially important to help parents understand the value of appropriate discipline in shaping their children's self-esteem. Information about discipline in the media may be confusing and contradictory and often supports the unfounded approaches of nonprofessionals. Starting when a child is 5 years old, physician-parent discussions should include the notion of monitoring.

Early in the physician-parent relationship, physicians may express their interest in behavioral problems by saying, "I am interested not only in your child's physical well-being but also in his [or her or their] growth and development and how he [or she or they] gets along with friends and family." They may then question parents about how children spend their days. During subsequent visits, pediatricians may say, "Parents of children of [child's name]'s age frequently worry about discipline. I wonder if you have any concerns." In making these inquiries, the physician may establish what factors, such as religious or ethnic beliefs, or family influences are shaping parents' decisions about discipline. Certain tools exist that can assist the primary care physician with counseling parents. One such model, Play Nicely, involves a multimedia educational program in English and Spanish that presents videos of hypothetical scenarios and has parents select from a list of options how they would manage the behavior. The program helps augment parents' repertoire of responses to their child's behaviors.

Corporal Punishment

The relationship among harsh punishment, use of corporal punishment, and child abuse has been addressed in a number of studies. The American Academy of Pediatrics has published extensively on the issue of corporal punishment and highlighted how approval of corporal punishment as an acceptable means of disciplining children has significantly decreased in recent years. It is of interest that the UN Convention on the Rights of the Child (1989) endorses banning corporal punishment and promoting positive discipline. Slapping, smacking, spanking, kicking, shaking, and throwing are all enumerated, as are other punitive measures. Data support physical discipline as being associated with subsequent aggressive behavior on the part of toddlers. There are also data linking corporal punishment with adverse childhood experiences (see Chapter 142). Scolding (yelling) is sometimes equated with harsh verbal abuse, especially if it is pervasive and may escalate to physical punishment. Receiving harsh verbal abuse before 13 years of age has been linked to adolescent behavioral and mental health issues.

Common Problem Behaviors

Common behavioral problems can be placed in 5 major categories.

1. **Problems of daily routine.** Such problems include the refusal of children to go about their daily activities, such as eating, going to bed, awakening at a certain time, and toilet training.
2. **Aggressive-resistant behavior.** Such behavior is characterized by negativism and includes temper tantrums and aggressive responses to siblings and peers. Some undesirable behavior can place children or those around them in danger or at risk for injury.
3. **Overdependent or withdrawal behavior.** This behavior is typical of children who are very attached to their parents These children find separation difficult, especially when beginning preschool.
4. **Overactivity or excessive restlessness.**
5. **Undesirable habits,** which include thumb-sucking, nail-biting, throat clearing, and playing with genitals (see Chapter 54).

Some of the listed behaviors are age appropriate, and physicians can help parents by counseling them about stage-related behavior, such as oppositional behavior in a 2-year-old and independence-dependence conflicts in a 3- to 5-year-old. Parents may be more tolerant of a particular behavior if they understand what is typical at a given age. Just because something is typical, however, does not mean that it should be tolerated. Physicians can suggest to the parents means of dealing with age-appropriate behavior (eg, placing breakable objects out of reach of toddlers).

Some behavioral problems reflect differences in childhood temperaments. Temperament is the biological predisposition to a style of behavior. William B. Carey, MD, has compiled a series of

temperament scales to assess children and adolescents of different ages. For example, some children are shy and have a hard time adjusting to new situations. If parents anticipate such problems, they are often less angry when difficulties arise. Parental expectations can vary with a child's sex. Boys may be permitted to act a certain way ("He's all boy!") that would be disapproved of in girls. Physicians can discuss such expectations at health supervision visits.

Physicians can also be particularly helpful in detecting and advising parents about disparities in the achievement of different developmental skills. Some children acquire motor skills before verbal skills, yet parents expect their children to be equally versatile in speech and movement.

Psychophysiology

All behaviors are modified by the responses and reactions of other individuals. The basic premise of discipline is to discourage unwanted behavior and to encourage desired behavior. This is accomplished by using techniques that are based on conditioning modalities.

Several factors contribute to an increased incidence of behavioral problems in children. Ten percent to 15% of all preschool-age children are raised in challenging or disrupted family situations. Homes may be affected by divorce, death, separation, violence, parental substance use, mental illness, or extreme poverty (see Chapter 141). Parental inexperience may also be a factor. In addition, families may have fewer social contacts than they once did because of greater mobility within society. As a result, families face greater social isolation and less availability of extended family.

Differential Diagnosis

In addition to providing anticipatory guidance about discipline, consider whether a specific behavior represents typical childhood behavior or an abnormality in behavior that warrants more specific intervention. Between 8% and 18% of behavioral disturbances may deserve physician intervention. More intensive management may be necessary for problems related to aggressive-resistant behavior and hyperactivity. Overactive behavior, which may exist as part of attention-deficit/hyperactivity disorder (ADHD), may be a sign of a significant underlying problem that warrants 1-to-1 intervention or the use of neuropharmacological agents (see Chapter 133).

Occasionally, children will be seen and noted to have bruises that were sustained during physical punishment. Although physical punishment is not illegal, the presence of significant bruises or injuries may warrant a report to child protective services.

Evaluation

History

The key component in the evaluation process is the assessment of the means parents use to discipline children (Box 50.1). To obtain this information, physicians may simply ask parents, "How do you get your child to mind you?" This question is designed to lead to a discussion of how parents interact with their children. A follow-up question could be, "What do you do if your child doesn't mind you?" This may help initiate a discussion related to parenting style and whether physical punishment is used to achieve adherence to parental rules. If parents have specific concerns, such as oppositional behavior, they should be questioned about the strategies they have used in their effort to discipline their children. It may also be useful to ask parents how they were disciplined as children to better understand their personal experience.

Box 50.1. What to Ask

Discipline

- What does the child do that the parents wish the child would not do?
- What do the parents do to stop unwanted behavior?
- Does the child usually obey the parents?
- What does the parent do if the child does not mind the parent?
- When and where does most of the unwanted behavior occur? Does it occur mainly if a child is tired?
- Which parent is responsible for disciplining the child?

Physical Examination

Children's behavior should be assessed during the office visit. A general physical examination is useful to check for any signs of physical abuse as well as to evaluate children's well-being. A developmental assessment is also helpful because it may delineate disparities in the achievement of certain skills. Some overly active children may warrant a more extensive psycho-developmental assessment to look for findings consistent with ADHD. Behavioral checklists may be used to evaluate children's temperament.

Laboratory Tests

No specific laboratory or imaging studies are indicated for children with discipline problems. Diagnostic studies are indicated if child abuse is suspected (see Chapter 144).

Management

Physicians should assist parents in establishing appropriate guidelines for disciplining their children and reinforce the role of parents as the source of authority (Box 50.2). It is important for parents to realize that total freedom, which may be seen in families with permissive parenting, may result in poorly controlled anxiety. Children mimic behavior, and parents should act as role models. If parents have temper tantrums when they are frustrated, their children may act in a similar manner. Consistency is also important. A system with a limited number of enforced rules is better than one with many different rules. In families in which both parents are working, especially if they have overlapping time schedules, consistency is sometimes difficult to attain, particularly if children are supervised by non-parental caregivers. Likewise, if parents are divorced and children are moving between 2 different households, rules may vary depending on which parent is caring for the child (see Chapter 149).

Box 50.2. Advice for Parents About Discipline

- Set rules.
- Set limits.
- Define consequences.
- Be consistent.
- Ignore trivial problems.
- Compliment desirable behavior.
- Take time out when angry.

Physicians should emphasize to parents that it is best to avoid power struggles. Children engaged in a struggle can often win because in some situations they have final control (eg, refusing to eat). Children should always be given the opportunity to graciously back out of a situation and save face. It is easier to avoid situations that lead to head-on confrontations than to gracefully emerge from them once the confrontation has occurred. Physicians can commend parents on appropriate handling of difficult situations, validate parental ability to handle their children appropriately, and guide parents on alternative strategies if there is a need to do so.

Physicians should remind parents that forestalling undesirable behaviors is easier than treating behavioral disorders once they arise. Reasoning is a useful modality, but it is unrealistic to expect infants and toddlers to have the cognitive skills to understand adult reasoning or to consistently respond to verbal commands or reprimands. Discipline should not only discourage bad behavior but also reinforce good behavior.

Following are 5 examples of reactive discipline: redirection, spanking, scolding, ignoring, and time-out and removal of privileges.

Redirection

Redirection is a simple and effective method in which the parent removes the problem and distracts the child with an alternative. This technique is frequently used to remove some object (eg, a valued knickknack) from the hands of an infant, replacing it with a toy. Parental patience, ingenuity, and enthusiasm facilitate this approach. This approach is also important in teaching children what is acceptable behavior. For instance, one cannot draw on the wall, but one can draw on a piece of paper. Children also respond to making tedious routines into a game. For example, children can be challenged to see who can get their clothes on faster or who can brush their teeth first. Parental creativity and energy often avert confrontations.

Spanking

Spanking involves inflicting physical pain, which can be successful in bringing about the immediate cessation or a decrease in problem behavior. Spanking is highly prevalent as a form of discipline, with between 70% and 94% of parents reporting using the practice. However, only 6% of pediatricians have a positive attitude toward spanking. Spanking is used more often for younger children and for boys and correlates with parental attributes such as age, education, socioeconomic status, and religious orientation. Spanking is often employed when other methods of discipline have failed to abort the unwanted behavior. Spanking tends to clear the air and get the punishment over with rather than producing a lingering guilt. To be truly effective, however, physical punishment must immediately follow the act. The "wait until Daddy comes home" approach is less effective because of the lack of temporal association. In addition, spanking tends to become situation-specific so that children associate a particular action with being spanked. This learning does not generalize to other situations. Spanking can teach children to be afraid of adults rather than to respect them.

Spanking, as well as other forms of physical punishment, can damage the parent-child relationship and have a long-term effect on a child's self-esteem. Parents may feel remorseful after spanking a child, and some acknowledge that they spank out of anger and frustration and question the efficacy of this modality. Most pediatricians discourage spanking as a means of disciplining children. Differentiation of physical punishment from child abuse can be difficult. In general, physical punishment using objects (eg, belts) and spanking on parts of the body other than the buttocks or thighs is unacceptable. Punishing a child by making them engage in physical exercise (eg, 200 jumping jacks) is also inappropriate. Spanking may be a precursor of later physical violence and subsequent abuse. Again, parents act as role models. Children should never be allowed to hit their parents. This makes children feel extremely insecure.

Devices that are marketed for child discipline and inflict physical pain on a child, such as a sudden sting (modified stun gun), are obviously never appropriate.

Scolding

Scolding involves the excess use of reasoning and explanations and is used by most parents as part of the discipline process. In families in which communication or interaction is minimal, scolding or verbal reprimands may result in an initial increase in inappropriate behavior because this is the only way children receive any attention. Verbal reprimands are more effective if used infrequently. Verbal reprimands should not be used during time-outs because they reinforce undesirable behavior.

Scolding, because of its negative focus, can be damaging to children's self-esteem. Scolding may be equated with yelling, verbal abuse, and harsh parenting practices. Scolding would be categorized by Rosenberg as "jackal language."

Ignoring

Ignoring represents the opposite of explaining and reasoning. This form of discipline is difficult to use successfully because parents must totally ignore children's behavior. If even the least flicker of recognition occurs, activity increases. A brief initial increase in unwanted behavior, a so-called response burst, may occur with ignoring. This disciplinary method works better in younger children.

Time-out and Removal of Privileges

Time-out, the form of discipline most often recommended, refers to time away from positive reinforcement. In sports, teams call a time-out to rethink what they are doing and to replan their strategies. Children are placed in a neutral or boring environment whenever they engage in inappropriate behavior. The time-out technique can be used to discourage undesired habits as well as inappropriate behavior. For example, parents may say, "You can suck your thumb, but you may only do it in such and such a room." This type of discipline is better than ignoring, especially if "ignored" children are receiving attention from siblings and peers. Children should understand the rules ahead of time and why the behavior is unacceptable. Once this is accomplished, time-out may occur without any warning.

A timer should be used, and children should stay in the time-out area for 1 minute per 1 year of age. An appropriate area must be selected. This area should be fairly boring, so children's rooms with their toys and electronic devices may not be appropriate. A laundry room, a corner, or a specific chair may be better. If children act unacceptably during the time-out, the timer should be reset. If children have to go to the bathroom during the time-out, they are allowed 1 trip. After they return from the bathroom, the timer is reset.

The use of the time-out method is not always easy. If the inappropriate behavior occurs in the morning when children are getting ready for school, time-out just encourages children's delaying tactics. "Beat the buzzer" is a better idea that may be used in such situations. With "beat the buzzer," the timer is set. For example, if children are dressed before the timer goes off, they may be rewarded for the behavior by being allowed to go to bed half an hour later, but if the buzzer "beats" them, they have to go to bed half an hour earlier.

Inappropriate behavior away from home presents an even greater challenge. These situations can be dealt with in numerous ways, particularly if the behavior problem involves temper tantrums. When children are crying or screaming uncontrollably, it is best to remove them from the embarrassment of the situation. This "manual guidance" often occurs in a supermarket, where children select something that parents do not wish to buy. Parents can often circumvent this problem by walking into the supermarket and saying, "If you are good during the whole trip, then I will get you something at the checkout counter." If children still have temper tantrums, they should be removed from the area and brought to a neutral place, such as the automobile or a restroom, and allowed to finish their crying and screaming. Inappropriate behavior can also be managed by "marking" time-out. This consists of putting a mark with a colored water-soluble marker on the child's wrist every time he or she engages in an inappropriate behavior. When the child returns home, the marks are totaled, and the time-out method is used. Once again, separating the undesirable behavior from the disciplinary consequence may limit the effectiveness of marking time-out.

Removal of privileges is a strategy applied with older children. Classically, this involves grounding a child, prohibiting television or video games, limiting the use of cell phones or other electronic devices, or loss of driving privileges. The privilege must be something of value to the child for this method to be effective.

Parents who report inappropriate behavior should be asked to keep a record of children's behavior for 1 to 2 weeks. This helps determine the nature of the behavior (eg, whether it is age-appropriate) and what is motivating it. Parents should be encouraged to talk to their children in a reasonable manner and to verbalize what they think children are feeling. They might say something like this: "It's terrible to be 3 years old and get so upset. You feel that you can't always get things you want. Once you grow up, you will be in charge. I am really sorry it is so hard for you right now." Physicians should tell parents that it is important to set limits for children and to avoid threatening, judging, and constantly criticizing children. Frequent threats, such as, "If you don't stop hitting your sister, you'll get a time-out," that are not carried out undermine the entire discipline process. To help foster compassionate communication, parents should ask themselves, "If someone said this to me, how would I feel?" Many parents have themselves been disciplined only with spanking and physical punishment and know no other means, and the advice that physicians offer is valuable.

There are models that can help parent improve their parenting skills. Triple P is an evidence-based proven parenting program, as are HealthySteps (www.HealthySteps.org) and Help Me Grow (https://helpmegrownational.org). Pediatricians are encouraged to be familiar with these resources and be able to share them with families.

Prognosis

Children raised in a supportive environment that teaches respect for others and self-control grow up as caring adults. Children who have been exposed to excessive physical punishment show aggressive behavior later. The physician is in an excellent position to influence parenting practices and child well-being.

CASE RESOLUTION

Further history should be elicited about the mother's disciplining techniques. It is also significant that the child's speech is delayed. The boy's ability to articulate his feelings may be limited, and a formal speech and hearing assessment is warranted. The preschool should be advised that the evaluation is underway. A report from the preschool concerning the boy's behavior is requested.

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CHAPTER 51

Temper Tantrums

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CASE STUDY

During a routine office visit, the parents of a 3-year-old boy express concern about his recent behavior. They report that whenever he is asked to do something he does not want to do, he throws a "fit." He cries fiercely, falls to the floor, bangs his hands on the floor, and kicks his feet until his parents give in. He often displays such behavior at bedtime or mealtime if he is asked to turn off the television or eat foods that he does not want. He has 2 to 3 such episodes per week. The parents state that their home life has not changed, and the boy's teacher reports that he displays no such behaviors at preschool.

Questions

1. At what age are temper tantrums common in children?
2. What aspects of child development contribute to temper tantrums?
3. How do parents' reactions encourage or discourage temper tantrums?
4. What appropriate management strategies may help control problematic tantrums?
5. What factors or aspects of problematic tantrums may indicate underlying pathology?
6. What referrals, if any, are appropriate for the management of temper tantrums?

Temper tantrums are common, normal, age-related behaviors in young children. To a certain extent, oppositional behaviors such as negativism, defiance, and tantrums are part of the normal progression toward self-reliance and independence. Toddlers need to assert their freedom and explore their environment, which often puts them at odds with the limitations imposed by society and well-meaning parents. Young children cannot appreciate that rules and limitations have been established in the interest of their own safety and well-being. They see only that their own desires have been thwarted, and they may react to this disappointment with intense emotions. Children are not simply upset because they cannot have their way. They are angry and frustrated, and they lose control over their emotions. During tantrums, children cry and scream uncontrollably. They may fall to the floor, bang their heads, kick their feet, pound their hands, and thrash about wildly. Some children may throw things, try to hit one another, or destroy property.

Such intense displays of anger may be a terrifying experience for children and parents. Some children use tantrums to gain attention, whereas others use them to achieve something or avoid doing something. Recurrent temper tantrums may strain relationships among parents, children, and other family members.

Epidemiology

Temper tantrums are noted most often in children who are 2 to 3 years of age, but they may occur any time between the ages of 1 and 5 years. Parental surveys reveal that approximately 20% of 2-year-olds, 18% of 3-year-olds, and 10% of 4-year-olds have at least 1 tantrum per day. Most children can express their feelings verbally by 3 to 4 years of age, at which point temper tantrums begin to taper off. Children who cannot express their feelings well with words, such as children with developmental delays, especially those with speech and language delays or with an autism spectrum disorder (ASD), are more likely to continue to have tantrums. Boys and girls are affected equally. Although temper tantrums are unusual in school-age children, they often reappear in the form of verbal tantrums during adolescence, when autonomy and independence once again become developmental issues.

Pathophysiology

Temperament, or adaptability and emotional style, affects the ease with which children adjust to environmental inputs and their reactions to these inputs. Temperament is the "how" of behavior, as opposed to the "why." It is innate rather than learned. Although inherent from birth, temperament may be modified in the early years by children's experiences and interactions. Stella Chess, MD, and Alexander Thomas, MD, identified 9 major temperamental traits based on their study of children's behavioral characteristics during the 1950s: activity level, rhythmicity (regularity), approach or withdrawal, adaptability, intensity, mood, persistence and attention span, distractibility, and sensory threshold. Three common patterns of temperament based on whether a child shows a greater or lesser degree of each of these traits are *easy* (high rhythmicity and adaptability with a positive mood), *slow to warm up* or *shy* (slow adaptability and tendency to withdraw initially in new situations), and *difficult* or *challenging* (low rhythmicity and adaptability, resulting in negative and intense reactions to the environment).

Appreciation of children's temperament allows parents to anticipate and understand their children's reactions, thereby affording them the opportunity to rethink how the parents interpret and respond to their children's behaviors. Ultimately, this knowledge

allows parents to guide children in ways that respect their individual differences. Temperament does not excuse children's unacceptable behaviors, but it does provide some insight into the origins of problematic behaviors, such as tantrums. For example, allowing extra time in the morning for the high–activity-level child with high distractibility and low attention span to get ready for school may avoid the daily negative interactions between parent and child. A discussion of temperament is not complete without noting that ultimately it is the "goodness of fit" between parental and child temperaments that is the key issue. What may appear to be a behavioral problem may in fact be a mismatch between parental and child temperaments (eg, a high-energy and high-intensity child may be quite challenging for the slow to warm up or shy parent). It is important to help parents appreciate that such mismatches in temperamental traits between themselves and their children do not necessarily represent problems in their children's character.

Understanding the child's level of maturity and the developmental tasks normally associated with the toddler and preschool years, which is when temper tantrums most often occur, facilitates further understanding of tantrum behavior. Young children who are exploring the world and developing a sense of autonomy think primarily in egocentric terms. They view reality from their own perspective and are unable to appreciate the perspective of other individuals. Only as they mature and enter school do they learn to recognize the position of others and begin to develop a sense of morality—of right and wrong. Toddlers may become frustrated or angry because of their lack of control over the world, their inability to communicate, or limitations of their cognitive and motor abilities, which do not allow them to accomplish desired tasks. Unlike adults, who can verbalize frustrations or simply walk away from unpleasant situations, young children have neither the sophisticated ability to articulate their feelings nor the freedom to walk away. Therefore, they may react to disappointments with temper tantrums. With cognitive and emotional maturation, children should gradually learn to exhibit more emotional control and/or use language to express themselves. If caregivers consistently reinforce tantrum behavior, however, such as by "giving in," this maturation process may be delayed.

Temper tantrums may be classified as normal or problematic based on their cause, frequency, and characteristics. *Normal tantrums* can simply be demands for attention or signs of frustration, anger, or protest. In the interval between tantrums, the child's disposition and mood are normal. The well-behaved 3-year-old boy who has an occasional tantrum after the birth of a sibling, the girl age 2 years 6 months who throws a tantrum to express frustration because no one understands what she is trying to say, and the 2-year-old boy who cries uncontrollably because he cannot complete the puzzle he started or run fast enough to keep up with his 4-year-old brother are all examples of normal tantrums. A typical reason for an avoidance-type tantrum is not wanting to go to bed at bedtime. All types of tantrum are more common when children are tired, ill, or hungry, because their ability to cope with disappointment and frustration is limited under these circumstances.

Frequent tantrums (>5 per day) and tantrums that result in destruction of property or physical harm to the child or others are signs of *problematic tantrums* (Box 51.1). These tantrums may result from factors that are beyond the child's control, such as parental problems, school difficulties, or health-related conditions (Box 51.2). For example, the child with unrecognized hearing loss may be performing poorly at school and resort to tantrum behavior in frustration. Marital discord or domestic violence may create anxiety for a child, which may manifest as frequent or destructive tantrums. Additionally, problematic temper tantrums may be a symptom of an underlying psychiatric or neurodevelopmental condition.

Differential Diagnosis

Temper tantrums are readily recognizable because of their classic pattern in which a child becomes frustrated, reacts physically, and cries or screams.

Box 51.1. Features of Problematic Tantrums

- Tantrums that persist or get worse beyond 4–5 years of age
- Frequent tantrums (>5 per day)
- Tantrums lasting more than 15 minutes
- Persistent negative mood or behavior in intervals between tantrums
- Recurrent tantrums at school
- Destruction of property during tantrums
- Harm to self or others during tantrums
- Other behavioral problems (eg, sleep disorders, aggressive behaviors, enuresis)

Box 51.2. Underlying Causes of Problematic Tantrums

Parent-related Factors

- Marital discord
- Abusive behavior toward children
- Domestic violence
- Substance abuse
- Depression
- Inappropriate parental expectations

Child-related Factors

- Developmental or learning disabilities
  - Hearing loss
  - Speech and language delays
  - Autism spectrum disorder
- Mood disorders (eg, depression, disruptive mood dysregulation disorder)
- Disruptive behavior disorders (eg, attention-deficit/hyperactivity disorder)
- Trauma-related impairment (eg, posttraumatic stress disorder)
- Temperament (eg, high persistence and intensity of response and slow adaptability)
- Illness
  - Unrecognized illness (eg, otitis media, sinusitis)
  - Chronic or recurrent illness

Evaluation

History

Obtaining a thorough history is essential (Box 51.3). Frequency of temper tantrums, circumstances that provoke them, a description of actual tantrums, and parental reaction must be ascertained. In some instances, this reaction may provide insight into why tantrums recur. Parental expectations should be assessed as well. Expectations that are inappropriate for children's age and developmental maturity may create unnecessary tensions between parents and children and result in tantrum behavior. Factors associated with problematic tantrums should also be assessed (Box 51.2).

It is important to remember that physicians usually see children whose tantrums are frequent, severe, or cannot be controlled by parents. First, the pediatrician must determine whether any underlying pathology may be contributing to the behavior and, if so, what parental or child factors may be provoking it. Second, the pediatrician must differentiate between normal and problematic tantrums (Box 51.1). Identification and remediation of the cause of problematic tantrums are the first steps toward cure.

Problematic temper tantrums can be a presenting symptom of an underlying neurodevelopmental or psychiatric condition, especially if the tantrums persist or worsen after 4 to 5 years of age despite the development of typical expressive language skills. Conditions associated with problematic temper tantrums include ASD, attention-deficit/hyperactivity disorder (ADHD), internalizing disorders, exposure to trauma, disruptive mood dysregulation disorder, and disruptive behaviors.

The child with ASD may have problematic temper tantrums related to the core deficits of the disorder, such as rigidity, difficulty with change, and perseverative interests (eg, a child who lines up toys may get upset if the arrangement is disrupted). In such situations, careful history about the "trigger" for the tantrum as well as an investigation into the child's developmental history (especially language and social skills) is warranted. For a more complete discussion of ASD, refer to Chapter 132.

Children with ADHD may react impulsively and lack the executive function skills necessary to regulate their emotional responses, which can precipitate problematic tantrums. Parent and teacher feedback should be solicited about behaviors of inattention and hyperactivity. For a more complete discussion of ADHD, refer to Chapter 133.

The child with an internalizing disorder, such as anxiety or depression, may exhibit generalized irritability or overreactivity with frequent temper tantrums. In the child with depression irritability, rather than sadness, may be the presenting mood symptom. Adolescent depression is discussed in Chapter 66.

The child with exposure to trauma can present with behavioral regression (eg, recurrence of temper tantrums) or changes in mood. If the severity or frequency of temper tantrums has recently increased, the pediatrician may screen for trauma by asking a simple question, such as "Since your last visit, has anything really scary or upsetting happened to your family or your child?" Cases of suspected traumatic exposure are best referred to a mental health professional for evaluation and treatment. Adverse childhood experiences and trauma-informed care are discussed in Chapter 142.

For the child with severe temper outbursts, the health professional should ask about characteristics suggestive of disruptive mood dysregulation disorder (Box 51.4). Referral to a subspecialist for further evaluation and treatment may be indicated. For more details about diagnostic criteria, see *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.

Disruptive behaviors, such as oppositional defiant disorder and conduct disorder, may present with severe temper tantrums in young childhood. High intensity of defiance, aggression to people and/or animals, self-harm, destruction of property, and difficulty recovering from tantrums occur more commonly in disruptive behavior disorders and warrant referral to a subspecialist.

Physical Examination

A thorough physical examination is appropriate, as is a developmental assessment to determine if the child exhibits findings such as speech delay or behavioral signs consistent with ASD or ADHD. Typically, the physical examination is normal.

Box 51.3. What to Ask

Temper Tantrums

- How often does the child have temper tantrums?
- What circumstances provoke the tantrums?
- How does the child behave during the tantrums? What does the child do?
- How does the child behave in the interval between tantrums?
- How do the parents react to the child during the tantrums? What do they do or say?
- Are parental expectations consistent with the child's developmental stage?
- Have there been any changes at home or school (eg, birth of a sibling, new school)?
- Is the child having any other behavioral or development-related problems (eg, enuresis, sleep difficulties)?
- Are there any other signs or symptoms of an underlying psychiatric or neurodevelopmental condition?

Box 51.4. Characteristics of Disruptive Mood Dysregulation Disorder

Temper Outbursts

- Are verbally and/or behaviorally disproportionate to the situation
- Are developmentally inappropriate
- Occur ≥3 times per week
- Occur in a child who is irritable or angry between tantrums
- Last for a defined time period
- Are not related to other mental health issues such as depression, medication, medical, or neurological conditions

Derived from *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.

Laboratory Tests

No laboratory tests are indicated in the assessment of the child with temper tantrums. Routine tests that are age-appropriate and suggested as part of health maintenance are appropriate.

Management

Health maintenance visits are an ideal time to provide anticipatory guidance on tantrums and discuss strategies to prevent or minimize this behavior. Parents typically report that their children become defiant and difficult to manage during the "terrible twos." At the 12- and 15-month visits, the physician should alert parents that this period is approaching and remind them that it is a normal part of development. Preventive strategies should be discussed, such as childproofing the home to minimize unnecessary conflicts. Additionally, parents can give young children frequent opportunities to make choices, such as which color shirt to wear or which of 2 foods to have for lunch. These opportunities allow children to exercise independence and autonomy in a positive rather than a negative manner. The physician can provide reassurance that this unpleasant stage will pass; children eventually become more cooperative and agreeable. Punishment is not the solution to temper tantrums (see Chapter 50).

A parent may inadvertently reinforce negative behaviors by primarily giving attention to the child during the moments the child is misbehaving. Setting aside special time between parent and child on a regular basis gives children a close connection with parents without having to misbehave. Similarly, *time-in* is a strategy in which the parent, upon noticing that the child's behavior is beginning to escalate, spends 5 to 10 minutes soothing and comforting the child in an effort to mitigate the emerging negative behavior.

Parents should be advised that helping children learn self-control and how to manage anger are keys to managing temper tantrums. To expect that a child will never become angry is unrealistic. Instead, children should be taught how to vent their anger and frustration in an acceptable manner, such as articulating their feelings or hitting a designated punching bag or pillow. As children mature, their ability to verbalize their feelings increases, but even young children can say, "Me angry." Physicians should emphasize that it is important for parents to remain calm during children's temper tantrums. Shouting and spanking indicate to children that parents are also out of control. Children feel more secure if the adults around them are calm and in control.

Different types of temper tantrum may require specific treatment and management strategies. A parent can prime a child by outlining expectations before common triggers occur, such as explaining before going to into a store that they are not going to buy a toy. Parents should be supportive of a child who is having a tantrum resulting from frustration or fatigue by letting the child know that the parent understands. The child's energy should be redirected into activities the child can do well. Parents should be encouraged to praise positive behavior, for example, completing tasks properly or managing anger in an acceptable fashion. They should ignore some tantrums, such as those for the purpose of attention seeking or wanting something. The child with no audience has no need to perform. Time-outs may also be used in such situations (see Chapter 50). Parents should not give in to children's wishes, because doing so may reinforce tantrum behavior. Physical movement of children to where they belong may be necessary if they are refusing to do something (eg, bed for the child who is refusing to go to sleep at bedtime) or in danger of hurting themselves. Holding children who are raging may give them a sense of security and help calm them. If temper tantrums occur outside the home, it may be necessary to accompany children to a quiet, private place, such as an automobile, until they calm down. Distracting children by suggesting another activity or pointing out something of interest in the environment may also interrupt the unwanted behavior. Corporal punishment is associated with increased aggressive behavior and loses potency with repeated administration. The American Academy of Pediatrics strongly discourages striking a child, including spanking.

If parents continue to struggle with their child's temper tantrums, referral to a parenting program should be considered (Table 51.1). Several parenting programs have demonstrated efficacy in decreasing disruptive behaviors and temper tantrums and may be available at community centers, parent support centers, and mental health facilities.

Table 51.1. Programs for Parents of Children With Temper Tantrums

Name of Program	*Child Eligibility*	*Comments*
The Incredible Years (www.incredibleyears.com)	Different groups for infant, toddler, preschool, and school age (up to 12 years)	Parenting classes provided in small group setting Course duration is 12–20 weeks Includes children's group for older children Programs also available for teacher training
Triple P—Positive Parenting Program (www.triplep.net)	Birth–16 years of age Multiple delivery methods to match specific needs Separate modules available for children with disabilities, medical concerns, and divorce	Range of services, including public seminars, telephone consultation, targeted counseling, small group learning sessions, online instruction, and 1-to-1 consultation
Parent-Child Interactive Therapy International (www.pcit.org)	Treatment modality for children with attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder	Averages 14 sessions lasting 1–2 hours each

CASE RESOLUTION

The child seems to be having normal, age-appropriate tantrums. The boy's tantrums occur when he is asked to do something that he does not want to do. In these situations, the parents should try to ignore the tantrums as much as possible and not give in to the child's wishes.

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CHAPTER 52

Breath-Holding Spells

Geeta Grover, MD, FAAP, and Peter Jinwu Chung, MD, FAAP

CASE STUDY

A 15-month-old girl is brought to the office because of parental concern about seizures. In the past month she has passed out momentarily 3 times. Each episode seems to be precipitated by anger or frustration on her part. Typically, she cries, holds her breath, turns blue, and passes out. Each time she awakens within a few seconds and seems fine. The medical history and family history are unremarkable, and the physical examination is entirely within normal limits.

Questions

1. What are breath-holding spells?
2. What is the differential diagnosis of breath-holding spell?
3. What, if any, laboratory studies are indicated in the evaluation of breath-holding spells?
4. What measures can be taken to prevent breath-holding spells? Are anticonvulsant agents necessary?
5. What are the effects of breath-holding spells on family functioning?
6. What, if any, are the long-term sequelae of breath-holding spells?

Breath-holding spells (BHSs) are a benign, recurring condition of childhood in which anger or pain produces crying that culminates in noiseless expiration and apnea. The frequency of BHSs, which are involuntary phenomena, is variable and ranges from several episodes a day to only several episodes per year. Although the spells are innocuous, they usually provoke fear and anxiety among parents and caregivers because children often turn blue and become limp. The diagnosis usually can be made on the basis of a characteristic history and description of the episode; however, the possibility of seizures should be considered.

Epidemiology

Breath-holding spells occur in approximately 5% of all children between ages 6 months and 6 years, but they are most common in children between 12 and 18 months of age. Most children with BHS will have experienced their first episode by 18 months of age and nearly all will have done so by 2 years. Although BHSs have been described in children younger than 6 months, occurrence in such young infants is uncommon. Boys and girls are affected equally. Approximately 25% of patients have a positive family history for BHSs.

Clinical Presentation

The typical clinical sequence of the major types of BHSs is described in the Pathophysiology section of this chapter and in Box 52.1. After a spell, the child may experience a short period of drowsiness.

Pathophysiology

Breath-holding spells may be classified as 1 of the nonepileptic paroxysmal disorders of childhood. These recurrent conditions, which have a sudden onset and no epileptiform focus, resolve spontaneously. Other disorders in this heterogeneous group include syncope, migraine, cyclic vomiting, benign paroxysmal vertigo, paroxysmal torticollis, sleep disorders (eg, narcolepsy, night terrors, somnambulism), and shudder attacks.

The 2 major types of BHS are cyanotic and pallid. Approximately 60% of children with BHS have cyanotic spells, 20% have pallid spells, and 20% have both types. Most commonly, affected children experience several spells per week. Approximately 15% of children with BHSs have complicated features. Complicated BHSs are defined as a typical BHS followed by seizure-like activity or rigid posturing of the body. Unlike the postictal period of epileptic seizures, prolonged periods of lethargy or drowsiness following spells are uncommon.

Pallid spells are similar to cyanotic BHSs with some exceptions. Pallid episodes are more commonly provoked by minor injury, pain, or fear rather than frustration or anger; the initial cry is minimal prior to apnea and loss of consciousness; and children become pale rather than cyanotic. In pallid BHSs, children often lose consciousness or tone after only a single gasp or cry, whereas in the cyanotic form, the period of apnea prior to loss of consciousness is much longer.

Etiology

Although the spells are triggered by identifiable stimuli, they are involuntary phenomena. It is believed that loss of consciousness in the cyanotic and pallid forms is caused by cerebral anoxia. The mechanisms of the 2 types of BHS are different. The processes involved in cyanotic BHS are not clear. Proposed mechanisms include centrally mediated inhibition of respiratory effort and altered lung mechanics, which may inappropriately stimulate pulmonary reflexes, resulting

Box 52.1. Diagnosis of Breath-Holding Spells

- Identifiable precipitating event or emotion
- Brief duration
- Color change, if present, prior to loss of consciousness and rhythmic jerking of extremities
- Rapid restoration of full activity
- Normal neurologic examination

in apnea and hypoxia. In the pallid form, the pale coloration and loss of tone are thought to result from vagally mediated severe bradycardia or asystole. Pallid spells have been spontaneously induced in the electroencephalogram (EEG) laboratory using ocular compression to trigger the oculocardiac reflex. Vagally mediated bradycardia or asystole lasting more than 2 seconds has been produced by this maneuver.

An association between iron deficiency anemia and BHSs has been recognized for many years but is poorly understood. It may be related to the importance of iron in the function of various enzymes and neurotransmitters in the central nervous system or because children with anemia have decreased cerebral oxygenation, making them more susceptible to BHSs.

Although children with BHSs have not been shown to have higher rates of psychiatric conditions compared with their otherwise healthy peers, they are more likely to exhibit difficult temperamental traits, including increased intensity of reactions and general states of anger, annoyance, and/or irritability. Mothers of children with BHSs have been shown to have higher rates of anxiety, depression, stress, and family functioning problems than mothers of children without BHSs. Breath-holding spells are also associated with stressful life events during pregnancy, although the mechanism and directionality of this association is not known.

Differential Diagnosis

The differential diagnosis primarily includes seizures and syncope secondary to cardiac arrhythmia or a vasovagal episode. Although vasovagal syncope, like BHS, may be provoked by fear or pain, it is uncommon in children younger than 12 years. Three factors may help differentiate BHSs from true epileptic seizure activity. First, spells usually are provoked by some upsetting event or emotion, unlike seizures, which generally lack a recognizable precipitating event. Second, episodes are brief in duration and are followed by rapid restoration of full activity. Third, color change precedes loss of consciousness and rhythmic jerking of the extremities, whereas in the typical epileptic seizure, convulsive activity and loss of muscular tone usually precede change in color. Box 52.2 shows the differential diagnosis of BHSs.

Evaluation

History

History alone may be diagnostic (Box 52.3). A family history of BHSs should be obtained. It is essential to record a detailed history of the suspected breath-holding episode. The sequence in which the events occurred may help differentiate BHSs from epileptic seizures.

Box 52.2. Differential Diagnosis of Breath-Holding Spells

Central Nervous System
- Seizures (ie, epilepsy)
- Occult or overt brain stem lesions (causing dysfunction within the pontomedullary area)
- Benign paroxysmal vertigo

Cardiovascular
- Cardiac arrhythmia (eg, long QT syndrome)
- Syncope (orthostatic or vasovagal)

Miscellaneous
- Gastroesophageal reflux/Sandifer syndrome
- Cataplexy (ie, transient loss of muscle tone associated with narcolepsy); rare before adolescence)
- Central or obstructive apnea
- Factitious disorder imposed on another (ie, Munchausen syndrome by proxy)

Box 52.3. What to Ask

Breath-Holding Spells
- What happened before the episode?
- Was the child crying?
- What was the child's color before and during the episode?
- Was the child lethargic after the episode?
- Does the family have a history of breath-holding spells?

Physical Examination

The child should undergo a complete physical examination, including a thorough neurologic evaluation. Focal neurologic signs or evidence of structural lesions, such as meningomyelocele or hydrocephalus, may be suggestive of a diagnosis other than BHSs.

Laboratory Tests

If the history is consistent with BHSs and the physical examination is normal, laboratory evaluation is usually unnecessary. Because of the association of BHSs with iron deficiency anemia in some children, it is appropriate to determine a hemoglobin level. An EEG may be obtained if the physician is concerned about the possibility of epileptic seizures. The interictal EEG is normal in the child with BHSs, whereas it is often abnormal in the child with epilepsy. In both forms of BHS, during attacks the EEG shows generalized slowing followed by flattening; this pattern is characteristic of cerebral anoxia. It is unusual to capture a BHS during the EEG, however. Simultaneous EEG and video recordings can be quite useful in helping to distinguish BHSs from seizures, especially in the child with

frequent episodes. An electrocardiogram may be obtained if there is any question about cardiac arrhythmia (eg, long QT syndrome).

Management

Management of BHSs includes parental support and reassurance. Breath-holding spells may be extremely frightening for parents to witness, especially if the episodes are routinely associated with loss of consciousness or seizure-like activity. Parents should be told of the involuntary nature of the attacks and cautioned against reinforcing the spells by giving in to the child's wishes. They should be advised to avoid unnecessary confrontations with the child. It is impossible to ensure that the child will never be frustrated or injured, however. Instead, parents should be encouraged to address the episodes in a matter-of-fact manner and continue using age-appropriate discipline. They should be reassured that the long-term prognosis is excellent. Research has demonstrated that psychoeducation about the disorder can reduce the level of anxiety, depression, and stress experienced by the caregivers; therefore, the physician may wish to consider screening caregivers for mental health concerns and referring them to the appropriate supportive services.

For a subset of children with iron-deficiency anemia and BHSs, iron therapy may be effective in the management of cyanotic and pallid BHSs. More recent research has demonstrated that iron supplementation, even in the absence of iron deficiency/insufficiency, may be effective in reducing the frequency of BHSs.

Referral to a neurologist, cardiologist, or psychiatrist may be considered for the child with frequent episodes or for complex cases. Pharmacologic therapy usually is not necessary, but atropine sulfate may be considered in the treatment of children with frequent pallid BHSs because of the anticholinergic action of atropine. Anticonvulsant agents are not effective. Successful cardiac pacemaker implantation has been performed for complex cases of pallid BHSs with severe and frequent spells associated with seizures, life-threatening bradycardia, or asystole. Case reports have noted the successful management of pallid BHSs with fluoxetine or a combination of glycopyrrolate and theophylline in small cohorts of patients. Finally, several blinded, randomized controlled trials performed outside the United States have demonstrated efficacy of piracetam in the management of BHSs, although this medication is not approved for any use by the US Food and Drug Administration.

Prognosis

Breath-holding spells resolve spontaneously in most children by 5 to 6 years of age. Approximately 50% of cases resolve by 4 years of age, and 90% resolve by 6 years of age. Neither pallid nor cyanotic BHSs are associated with an increased risk for developing epilepsy, although children with pallid BHSs do have an increased incidence of developing syncopal attacks in adulthood.

CASE RESOLUTION

The child has a history and physical examination suggestive of BHSs. The girl's episodes are consistent with cyanotic BHS. The episodes are preceded by an identifiable emotion, brief in duration, and followed by a rapid recovery of normal consciousness and activity. Assessment of the hemoglobin level revealed mild iron deficiency anemia. The child received iron therapy, and the parents were reassured about the benign nature of BHSs.

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CHAPTER 53

Fears, Phobias, and Anxiety

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CASE STUDY

A 5-year-old girl is brought into the office by her mother, who complains that her daughter has been afraid to sleep alone since the occurrence of an earthquake. The house did not sustain any significant damage, but the entire family was awakened. The mother says that the girl has become more timid. As nighttime approaches, she becomes particularly fearful. She will not stay in her bed, and she is comforted only by sleeping with her parents. In addition, the girl has begun bed-wetting since the earthquake, and the mother wonders whether she should put her daughter in diapers. The physical examination, including vital signs, is normal, except for the observation that the child is very clingy and whiny.

Questions

1. What are normal childhood fears and when do these fears commonly occur?
2. What strategies are used to deal with these fears?
3. What are phobias? What are social phobias?
4. What is school phobia, and how is it best handled?
5. What are common anxiety disorders in children and adolescents?
6. How can families deal with childhood disturbances that emerge after natural and artificial disasters?

Fears are normal feelings that cause emotional, behavioral, and physiological changes that are essential for survival. Fears are associated with psychological discomforts, such as a negative, unpleasant feeling. Children may develop fears in response to actual events (eg, earthquakes) or as a result of the temporal association of 2 events (eg, seeing a scary movie on a rainy day and then becoming afraid of rain). Some fears seem to be innate, and others seem to be developmental. Children fear different things at different ages. For example, school phobia is sometimes particularly problematic in young, school-age children. Worry is the cognitive manifestation of fear and anxiety.

Phobias are overwhelming, intense, highly specific, and often irrational fears. The *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition, defines a *phobia* as excessive anxiety accompanied by worry occurring more often than not, for at least 6 months and associated with 1 or more of the following: restlessness, easy fatigability, difficulty concentrating, irritability, tense muscles, and disturbed sleep. Childhood phobias can be divided into 5 categories: animals (eg, spiders, snakes, dogs), natural environment (eg, heights), medical related (eg, doctors, dentists, injections), situations (eg, flying), and other (eg, loud noises, rain, thunder). Specific phobias are often managed by avoidance and may not present to the physician for treatment. Social phobias (also called social anxiety disorders) are specific to social situations that arouse intense concerns about humiliation or embarrassment. Fear of speaking in public may represent a social phobia. Selective mutism involves children who are able to speak but are unable to do so in certain settings, such as school. This probably represents 1 form of a social phobia. When these fears are combined with avoidance behavior, they may be incapacitating. *Anxiety* refers to fear without a definable source. It is characterized by a physiological response and may be perceived as a vague feeling of uneasiness, apprehension, and foreboding of impending doom. A child may experience an anxiety problem where there is significant but not severe distress and an anxiety disorder when the distress is excessive or functioning is impaired. Fifteen percent to 20% of youths have anxiety disorders, the most prevalent psychiatric condition in children and adolescents. Girls are twice as likely to develop anxiety disorders as boys. There is often a positive family history of anxiety disorders, which is felt to be related to a genetic predisposition and environmental factors. Children with autism spectrum disorder have an increased incidence of anxiety and anxiety-related disorders (see Chapter 132).

Different strategies are useful for dealing with different fears. It is important for parents not to trivialize these fears or reinforce them but to empower children to deal with them.

It is also important to realize that parents sometimes foster fears by using threats with children, such as, "The doctor will give you a shot unless you eat your spinach," or "The boogeyman will get you." By fostering fears, the parents are also fostering dependency. Parents lack the imagination that children have and find it difficult to understand the degree of fear that children experience.

The opportunities for primary care physicians to counsel families about childhood fears has increased over the past decades related to a number of catastrophic events, such as the terrorist attacks of September 11, 2001 (9/11), hurricanes Katrina and Sandy, the earthquake in Haiti, the tsunami in Sri Lanka, and tornados in the midwestern United States. Acts of violence, such as multiple mass shootings, often at schools (eg, Columbine, Sandy Hook, Virginia

Tech, Marjory Stoneman Douglas High School), also create fear and anxiety in children and adolescents who witness these events on television and through messages posted on social media. It is important to recognize the pervasiveness of mental health sequelae following disasters and the factors that influence the prevalence of these disturbances. One percent of children in New York, NY, lost a relative on 9/11. There is a greater risk of mental health sequelae if there are poor social supports or a prior history of psychopathology or if the child is fearful or shy by nature. Natural disasters have a lesser effect than intentional ones. While many of the recent disasters have been acute and unexpected, there are children who are continuously exposed to what has been called "process trauma" in the form of war, detention of children and families seeking political asylum in the United States, and child abuse.

Epidemiology

Fears follow a developmental pattern (Box 53.1). Neonates are believed to have no fear, although young infants whose faces are covered with a blanket struggle to toss off the blanket. Infants who are 6 months of age exhibit what is known as *stranger anxiety* in response to unfamiliar persons, places, or objects. To combat this anxiety, infants seek refuge with a parent. Stranger anxiety becomes equated with separation anxiety and reaches a peak at 2 years of age. Children between 6 months and 2 years of age are also frightened by loud noises and falling or quickly moving objects.

Children between the ages of 2 and 5 years are in what is termed the *age of anxiety*. They fear many things, including animals, abandonment, loud noises, and darkness. Children in this age group are particularly fearful of physicians, hospitals, and getting hurt. Young children are afraid of those who are physically disabled, who represent bodily injury, and monsters and scary movies. They sometimes displace their anger onto monsters and witches and attribute to these imaginary characters the bad feelings they are experiencing. Children in this age group have strong imaginations, which makes it difficult for them to differentiate fantasy from reality.

Children between 6 years of age and adolescence tend to have more abstract thoughts, and their fears are less relevant to physical immediacy. These children are afraid of the death of their parents or the burning of their home. They also fear war, growing up (expressed as "How will I know what to do?"), going into the next grade, being alone or kidnapped, and the divorce of their parents. Children in this age group are often reluctant to bother their parents with their fears, and they can easily misinterpret parental concerns when they overhear parental conversations. *Separation anxiety*, which may manifest as school phobia and may be referred to as separation anxiety disorder, may occur in school-age children. The prevalence is estimated at 3.2% to 4.1%, although up to 50% of third graders report separation anxiety symptoms. *Separation anxiety disorder* is defined as developmentally inappropriate, excessive anxiety precipitated by actual or anticipated separation from home or family. Affected children develop physical complaints (eg, stomachaches) on school days. The parent-child relationship may be disturbed or made insecure (eg, marital discord, maternal illness), and the child is fearful of leaving the parent alone. Childhood school phobia and parental history of panic attacks and agoraphobia may be associated.

Fears during adolescence relate to social functioning, such as public speaking or talking to members of the opposite sex. Older children are also concerned about school failure and physical injury. They have many of the same fears expressed by school-age children, although phobias are uncommon. Social phobia is a distinct entity and is different from shyness, as reported in a recent study of adolescents. Social phobia is a potentially impairing psychiatric disorder. Overall, phobias occur in less than 1.7% of the general population but are reported in 13% of children with other emotional or behavioral problems.

Anxiety disorders are rare in childhood but more common during adolescence. They may include panic attacks, which involve the sudden onset of intense fear or discomfort associated with physiological symptoms such as palpitations and shortness of breath. Fear about a panic attack may lead to agoraphobia (ie, the avoidance of going away from home). Posttraumatic stress disorder (PTSD) involves a set of symptoms that recurs after a person has experienced a traumatic event. Symptoms include intense fear, helplessness, or a sense of horror. The person reexperiences the trauma, avoids circumstances that are reminiscent of the trauma, and is in a state of hyperarousal. It is estimated that 5% of men and 10% of women have a lifetime prevalence of PTSD.

Box 53.1. Common Fears During Childhood

- Neonates: no fears
- 6 months–2 years: separation anxiety, loud noises, quickly moving objects, the dark
- 2–5 years (ie, age of anxiety): animals, abandonment, loud noises, darkness, physicians, hospitals, getting hurt, monsters, witches, ghosts, storms
- 6 years–adolescence: death (parental death), parental divorce, natural and artificial disasters, growing up, school performance (going into the next grade), war
- Adolescence: social situations, school performance, health, public speaking

Pathophysiology

Fear has its basis in a series of psychophysiological reactions, which are mediated through a series of neurotransmitters. The reaction is often referred to as the fright/flight response and is critical for survival. The response is regulated through the limbic system. Elevated levels of certain transmitters, such as γ-aminobutyric acid and norepinephrine, are associated with feelings of anxiety. Excess serotonin has also been related to anxiety disorders.

Studies on the neurobiology of pediatric anxiety disorders demonstrate dysfunction in the amygdala prefrontal-based circuits. The amygdala is responsible for the initiation of the central fear response and is noted to be "overactivated" in magnetic resonance imaging of

individuals with anxiety disorders. The prefrontal area helps regulate amygdala activity. Other areas of the brain have also been implicated in anxiety disorders in youth.

Differential Diagnosis

The challenge for physicians is to assess the etiology of the fear and to differentiate normal fears from those that may be signs of unusual stresses or signs of psychopathology. Appropriate fears represent a real reaction to a real danger. As a rule, children are more resilient than adults and recover more rapidly from traumatic events. However, children are prone to inappropriate fears, which may develop for a number of reasons.

Inappropriate fears may occur because of operant conditioning, in which a conditioned stimulus becomes associated with another object. Fear of the other object becomes reinforced through this association. Inappropriate fears may also develop in a child whose parent has the fear (modeling) or through witnessing a fearful event in the media (informational). True phobias represent neuroses and may occur in more than 1 family member.

School phobia, also called school refusal, may occur under 3 distinct conditions. Not uncommonly, young children who are entering school for the first time are frightened. This fear is a normal component of separation anxiety, which usually resolves within a few days of starting school. This is also referred to as adaptive anxiety. In contrast, older children may experience school phobia because they are truly afraid of a school situation. They may fear a teacher, violence, or a bully. To avoid the problem, children may actually request to change classrooms or schools. It is important to talk with children to find out what is behind their fear of school.

Some children who seem fearful of school, however, are actually concerned about parental separation (ie, separation anxiety). Frequently, these children enjoy school and miss it when they are absent. Absences occur when children's feelings of separation from parents are so intense that they do not allow them to function well in school settings. Children are worried that something bad will happen to them or to their parents when they are apart. This separation anxiety disorder may result from parental illness or parents' fostering dependency in children. Children then see parents as vulnerable and are uncomfortable about leaving them alone. To qualify as an anxiety disorder, the symptoms must last at least 4 weeks.

School phobia is the third leading cause of school absenteeism after transient illness and truancy. Fifty percent of children with school phobia have other problems, including depression (28%), tantrums (18%), sleep disturbances (17%), obsessive-compulsive behavior (11%), other fears (10%), enuresis (3%), and learning disabilities (3%). Overall, school phobia has a good prognosis, although adolescents do not do as well as younger children, and individuals with a higher IQ have a poorer outcome. Twenty percent of parents of children with school phobia have a diagnosable psychiatric disorder. Issues of parent-child dependency are often a concern.

Another type of childhood fear concerns physicians and hospitals. Children have many concerns about what happens to them at the doctor's office. They are particularly fearful of needles. To children, needles represent possible mutilation. When asked to represent needles in drawings, children often portray needles as larger than themselves and very pointed. They comment that needles are sharp (eg, "Needles can make you pop, just like a balloon"; "Needles can also take out all your blood until you die"). In addition, children are preoccupied with what happens to their blood. One youngster commented, "They check out your blood to see if it's good or bad, and if your blood is bad, then it means that you need to have more tests." Another youngster thought that physicians were doing a "blood taste" rather than a blood test.

Hospitalization raises other issues concerning parental separation as well as painful procedures. As children adjust to hospitalization, they progress through 3 stages: protest, during which they complain about the hospital and cry; despair, during which they have given up hope that their parents will return; and detachment, during which they seem to be adjusting but actually have distanced themselves from their parents. Unrestricted visitation by family members and involvement of child life specialists mitigates much of the distress.

Evaluation

Physicians should explore the area of childhood fears and phobias at routine health supervision visits, even if parents do not have specific concerns. Sometimes parents are embarrassed by children's fears (eg, the fear of an older child to sleep without a night-light; the fear of dogs, which may preclude the child from visiting certain friends). Parents may not report children's fears unless these fears seem to be unusually intense. Practitioners may ask children, "What is the scariest thing you can think of?" If children are having difficulty providing details, physicians may ask them to name things that other children fear or to complete the sentence, "I feel afraid when...." Alternatively, practitioners may suggest things that other children may fear: "Do the kids you know seem to be worried about kidnapping?"

Several instruments have been used to assess the level of anxiety in children. These include the *Multidimensional Anxiety Scale for Children,* 2nd Edition; *Spence Children's Anxiety Scale*; and Screen for Child Anxiety Related Disorders. The latter instrument is in the public domain and readily available. It includes statements for children (eg, "I get scared if I sleep away from the house") that are then scored "Not True or Hardly Ever True" (0), "Somewhat True or Sometimes True" (1), and "Very True or Often True" (2). There is a separate page for parents that includes similar statements framed as, "My child gets...", rephrasing the statement that their child rated. Scores are added up and the total score, plus the items that scored high, help distinguish the nature of the anxiety; a score of greater than 25 indicates an anxiety disorder, with subcategories including panic disorder or significant symptoms, generalized anxiety disorder, separation anxiety disorder, social anxiety disorder, and significant school avoidance. Another instrument is a book called, *What to Do When You Worry Too Much: A Kid's Guide to Overcoming Anxiety.* This book suggests a number of strategies (eg, setting up a worrying time, not worrying if it's not the designated time) in addition

to discussing the origin of different worries (eg, "How do worries get started?").

History

The evaluation of children with specific fears demands a careful history that provides information about situations in which children are fearful (Box 53.2). Physicians should consider fears within a developmental context because many childhood fears are normal and experienced by all children. It is also important to look at changes in the family situation. Children sometimes develop what seem to be fears but in fact are behaviors designed to manipulate other family members. For instance, young children who sense marital discord may insist on sleeping with their parents as a way of ensuring that the parents are together rather than separate.

Physical Examination

A routine examination is warranted, but findings are usually normal. Such an evaluation, however, is particularly important if presenting complaints include symptoms such as abdominal pain, headache, or palpitations.

Laboratory Tests

As a rule, laboratory tests are not required unless the symptoms suggest an organic etiology, such as hyperthyroidism, as the cause of palpitations.

Management

Management of the fear or phobia is determined by the degree to which children are incapacitated. As a general rule, children should be empowered to conquer their fears. Children's books that address the issues of certain fears can help achieve this empowerment; for example, *The Berenstain Bears in the Dark* discusses specific worries such as fear of lightning and thunder. These books often explain the basis of such natural phenomena in easy-to-understand terms. Books also normalize particular fears and show how 1 character is fearful. Parents can recreate some of the sounds that children fear. For example, children who are afraid of the noise the wind makes are shown a teakettle from which hot steam blows through the whistle, creating the same noise as the wind. For fears about nuclear war, empowering children to become active, such as joining a nuclear protest group, may be useful.

Box 53.2. What to Ask

Fears and Phobias

- What fear does the child have? Exactly what does the child fear?
- Under what circumstances was the fear originally expressed? Did any changes in the child's life occur around the time that the fear appeared?
- Under what conditions is the fear currently expressed?
- How long has the child had the fear?
- How does the fear affect the daily living of the child and family?
- What has the family done to help the child deal with the fear?

Parents may feel helpless because they do not know how to deal with children's fears. Physicians should give them the necessary information. Children's fears should not be trivialized. Even if the fears are unfounded, they should be validated. When discussing fears with children, parents should always provide physical comfort and help children develop a sense of safety and security. In general, children should be questioned about whether they are fearful about a situation. The following 2 examples illustrate the proper handling of fears in children:

If children are visiting the dentist for the first time, it is appropriate for parents to ask, "Are you afraid?" If children reply, "Yes, a little bit," parents can say, "Almost everybody is afraid. Tell me what it is you're afraid of. Fear is a normal emotion, and I'm glad you told me about it."

Parents of children who express fear of imaginary characters can reassure children that they do not exist. In addition, parents can tell children what the parents would do if such characters did exist. For instance, the father of a little girl who was afraid of witches told her, "There are no such things as witches. But if there were, and they came into your room, I would punch them in the nose and punch them in the stomach and beat them up, and then there would be no more witches to hurt you." For those who would opt for a less violent approach, the parent could state: "I would tell any witch who came into your room, 'STOP! Go away. No witches allowed in here.' And the witch would run away, and I would slam the door!" By doing this, parents establish the reality of the situation and then also create a plan to deal with the problem should it actually happen.

Parents can also help to limit or reduce children's fears by minimizing their exposure to fear-provoking situations such as television shows or scary movies. These programs can be particularly frightening for some children, who should not watch them without adult supervision. Minimizing exposure to television is particularly important following a disastrous event. The recurrent images of planes flying into buildings on 9/11 were interpreted by children as repeated different attacks. Watching the nightly news can be anxiety provoking not only for children but for their parents. Even if a family chooses not to watch the evening news, "breaking news" including graphic images often appears on cell phones and other electronic devices automatically, intruding during the school day.

When dealing with children who have school phobia because of problems in school, it is important to determine if a change in school would be appropriate to facilitate their school attendance. This may be particularly appropriate in children whose schools are plagued with violence.

Cognitive-behavioral therapy (CBT) is reported to have the highest rate of success for dealing with anxiety-related conditions. Cognitive-behavioral therapy includes psycho-education, somatic management (eg, relaxation techniques), cognitive restructuring (ie, modifying negative thoughts), and exposure methods, including desensitization. The goal of the therapist is to teach the child alternative ways of viewing the feared object and of coping with the fear itself. Social Effectiveness Therapy for Children and Adolescents is geared to specifically address social phobia (social anxiety disorder).

Studies have demonstrated it is more effective than placebo and superior to fluoxetine on certain measures of social functioning. Mindfulness-based psychotherapies have also been incorporated into the management of anxiety disorders. The focus is on the development of mindfulness skills to help mitigate the symptoms associated with anxiety.

Medications such as antidepressants, anxiolytics, sedatives, and beta blockers have an unsubstantiated role in managing phobic disorders in children but may be indicated in other conditions, such as anxiety disorders.

When school phobia is linked to separation anxiety, a program of *desensitization or habituation (graded exposure)* is recommended. Desensitization may involve the participation of parents in the classroom for a time. When children acclimate and can tolerate some separation, mothers move to another area in the school, such as the principal's office. Next they go outside the school grounds. As children reestablish a sense of well-being in spite of the separation, the mothers gradually move farther and farther away. This solution is somewhat problematic for mothers who work outside the home. There is some research to suggest that children adjust more readily if they resume school immediately without the gradual withdrawal of their parent. Children with significant school phobia may need the assistance of child psychologists or psychiatrists.

Phobias may be treated using the concept of *flooding*, which consists of rapid, prolonged exposure to the feared item. For example, a child who is afraid of dogs is exposed to a friendly, docile, small dog while in the company of the child's parents. Alternatively, systematic desensitization, during which children are exposed to the feared objects over a series of weeks, coupled with relaxation techniques, is also used. Phobias usually require the help of mental health specialists. Selective serotonin reuptake inhibitors (see Chapter 134) have been found to be beneficial in the management of certain anxiety disorders in children and adolescents. They are noted to be effective for panic disorders, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, and PTSD. Benzodiazepines are safe and generally used on a short-term basis. Sedation is a frequent side effect, and there is the potential for misuse, tolerance, and drug dependence. Propranolol lessens the peripheral autonomic nervous system symptoms of social phobias and may be used for specific instances. Combined therapy involving CBT and medication is beneficial in some patients.

Children who must undergo hospitalization benefit from a prehospital visit, when possible. This visit familiarizes the child with the facilities and explains proposed procedures. Many hospitals have child life specialists who ease the adjustment of children as well as their parents to the hospital stay.

Prognosis

Most childhood fears resolve with time, nurturing, and reassurance. Most fears last only several weeks, and then new fears may develop. As a rule, specific fears should not last longer than 2 years, and the younger the child, the shorter the duration of the fear.

Prognosis is good for children with true phobias, with 100% resolution of monosymptomatic phobias. More significant anxiety disorders may persist into adulthood, at which time similar management involving CBT and medications may be indicated. Persistent anxiety disorders are associated with increased morbidity, including an increased risk for self-injurious behavior and suicide. Early recognition and appropriate management can significantly affect the prognosis of this common pediatric disorder.

CASE RESOLUTION

The girl's fear of sleeping in her bed was triggered by a significant environmental event. Although earthquakes are uncontrollable, the girl can be empowered to cope with manageable aspects of an earthquake as much as possible. She should be assured that in the same situation, many adults probably would also fear sleeping alone. The parents should stock a box with shoes, a flashlight, a radio, and water and place the box under the child's bed. In addition, they may have their daughter get into her bed and then shake it, simulating the jiggling that she would experience during an earthquake. The girl should also practice getting out of bed and standing in the doorway. To combat the child's fear of separation during times of natural disaster, the parents should reassure their daughter that they will all be together.

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CHAPTER 54

Thumb-sucking and Other Habits

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CASE STUDY

A 5-year-old boy is brought to the office because of thumb-sucking. His mother claims that she has tried nearly everything, including tying his hands at night and using aversive treatments on his thumbs, but nothing has worked. She reports that her son has been teased at school and has few friends. He is in good general health, and his immunizations are up-to-date.

His growth parameters are at the 50th percentile. Except for a callus on the right thumb, the physical examination is normal.

Questions

1. What are common habits in children?
2. What is the significance of transitional objects?
3. What are the consequences of common habits in children?
4. What are strategies used to break children of habits?
5. How are benign habits differentiated from self-injurious behaviors?

Habits are defined as somewhat complicated, repetitive behaviors that become automatized, fixed, and carried out easily and effortlessly. They are different from *tics,* which are rapid, repetitive muscle twitches involving the head, face, or shoulders. Tics are also referred to as habit spasms (see Chapter 130). Children have many habits that are characteristically discouraged, such as thumb-sucking, nail-biting, skin picking, nose picking, hairpulling (trichotillomania), rocking, biting other children, and teeth grinding (bruxism). Some habits, such as pica (the ingestion of nonfood substances), are potentially harmful. Children engage in most of these habits because of their soothing potential. In recent years, cutting, a form of self-injury in adolescents, has received attention. While not a habit in a traditional sense, cutting is described by teenagers as a way of dealing with stress and alleviating anxiety. One-third of children use transitional objects for comfort. Blankets or favorite toys are traditional transitional objects that represent an age-appropriate coping strategy. Most transitional objects are stroked, and the stroking often occurs in association with thumb-sucking. Transitional objects sometimes present a problem because children experience distress if these objects are lost or misplaced or need cleaning.

Epidemiology

Thumb-sucking probably represents the most common habit of children and is also reported in other primates, including chimpanzees. Up to 90% of children engage in this habit at some point. Prenatal ultrasonography has demonstrated in utero thumb-sucking in some fetuses. The median age for the onset of hand sucking is 54 minutes after birth, and 90% of newborns show hand-sucking behavior by the age of 2 hours. Forty percent of children between the ages of 1 and 3 years, 33% of children between the ages of 3 and 5 years, and 25% of children at the age of 5 years still suck their thumbs. Some children suck fingers rather than thumbs. Other oral behavior may involve lip sucking, lip biting, and toe sucking. Lip sucking and biting begin at about 5 to 6 months of age and occur in about 90% of infants. It is unusual for these actions to persist as habits. Toe sucking is noted in infants who are 6 to 7 months of age and is reported in 80% of typically developing infants.

Trichotillomania is a disorder once believed to be uncommon but now thought to affect 8 million Americans (about 5 in 1,000). The term, first coined in 1889 by French dermatologist Hallopeau, is derived from the Greek *thrix* (hair), *tillein* (pull), and *mania* (madness). The condition is an impulse control disorder in which alopecia develops from compulsive hairpulling. Hairpulling may involve hair from the head, eyebrows, eyelashes, or pubic area. Trichotillomania is reported from infancy into adulthood. In young children, boys and girls are equally affected, but in older children and adolescents, females outnumber males. In preschool-age children, trichotillomania is viewed as benign, similar to thumb-sucking. When the condition appears in older children (most common age of onset is between 9 and 13 years) the condition is more likely to persist into adulthood. The disorder is not associated with comorbid psychopathology, but there may be some association with mood disorders or attention-deficit/hyperactivity disorder. There is a condition in infants, called "baby trich," in which infants pull their mother's

hair when they are being held or nursed. This is considered typical exploratory behavior.

Rhythmic movement habits are stereotypical, repetitive behaviors that usually occur in infants younger than 1 year. Based on parental reporting, rhythmic movements are noted in up to 15% to 20% of the population. Rhythmic movements include rocking (about 19% of infants), when infants rock back and forth; jouncing (5%–10%), when they move in an up-and-down manner on their hands and knees so that the whole crib rocks; head rolling (8%); and head banging (5%). Rhythmic movements are seen more commonly in boys; the male to female ratio is 3:1. These habits usually occur with a frequency of 60 to 80 movements per minute, often when infants are tired, and last for less than 15 minutes before they fall asleep. In a recent study that used home videosomnography to assess the occurrence of sleep-related rhythmic movements in more than 700 infants and toddlers, the prevalence was significantly less, at only 2.87%.

Rhythmic movements have sometimes been referred to as *sleep tics*. These tics are reported in 20% of children, most often between the ages of 6 and 10 years. As a rule, tics are 3 times more common in boys than girls. They tend to be noted with increased frequency in children who are shy or overly self-conscious or have obsessive-compulsive tendencies. Tics usually occur when children are under stress.

Biting, an aggressive habit noted in toddlers, may be related to teething. It occurs more often in children with delayed language development.

Nail-biting (onychophagia) is deemed to be a sign of internal tension and affects 10% to 40% of children. Nail-biting begins between the ages of 3 and 6 years, and the peak age is 13 years. One-third of adolescents bite their nails, but 50% of these adolescents break the habit by the time they reach adulthood. When nail-biting persists into adulthood, it may be considered an oral compulsive disorder and classified under obsessive-compulsive and other disorders in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (*DSM-5*). The family history for nail-biting is often positive. Identical twins are concordant for the condition in 66% of cases. In contrast, the incidence in dizygotic twins is 34%.

Nose picking, noted in children and adults, is reported in more than 90% of individuals. In general, adults and older children limit nose picking to when they are unobserved, but younger children will pick their noses in public. There are no sex-based differences in the prevalence of nose picking. Nosebleeds are the most common complication of nose picking (see Chapter 90).

Pica is defined as the ingestion of nonfood, nonnutritive products. The peak prevalence of pica is between the ages of 1 and 3 years. The prevalence is increased in children of lower socioeconomic status, and the behavior occurs in 10% of children who present with lead poisoning. To meet the *DSM-5* criteria, pica must persist for longer than 1 month at an age when eating such objects is developmentally inappropriate and not part of a culturally sanctioned practice. The word *pica* is derived from the Latin word for the magpie (picave), a bird attributed with eating anything. Patients with pica may prefer specific substances to ingest, such as ice (pagophagia), soil (geophagy), or stones (lithophagia).

Teeth grinding (bruxism) is reported in 5% to 15% of children and frequently occurs during sleep. Boys are more commonly affected than girls, and the disorder seems to regress later in life. It is reported with increased incidence among children with developmental delays, including those with autism spectrum disorder. The cause is unknown, although it may be associated with malocclusion in some children. There is some evidence that sleep bruxism in childhood is associated with an increased incidence of exposure to secondhand smoke. The disorder may contribute to temporomandibular joint dysfunction and pain.

Self-injury has been reported in up to 20% of adults with intellectual disabilities. Autism spectrum disorder and the absence of speech are the highest associated risk factors. Nail-biting, head banging, and self-biting are frequently described associated behaviors. Severe self-injury related to biting is seen in Lesch-Nyhan syndrome.

Clinical Presentation

Children with common habits, such as thumb-sucking or rhythmic movements, may be brought to the physician with these particular complaints because the parent wants advice about stopping the behavior. Other children may present with consequences of habits, such as alopecia (trichotillomania), paronychia (nail-biting), or lead intoxication (pica). Whitlow (infection of the tip of the finger; also called felon) and, rarely, osteomyelitis of the distal phalanx have also been reported with nail-biting. Osteomyelitis should be considered in a nail-biting child who presents with an abscess of the finger. Hairpulling can be associated with hair ingestion, also referred to as trichophagia. Trichobezoars that can complicate trichotillomania associated with trichophagia may present with gastric outlet or bowel obstruction. Symptoms then include abdominal pain, anorexia, early satiety, nausea, vomiting, halitosis, and weight loss (Box 54.1).

Pathophysiology

Children engage in habits to reduce stress and provide comfort. Thumb-sucking is related to nonnutritive sucking. Although the initial purpose of sucking is nutritional, the pleasure associated with sucking reinforces the behavior. Infants who are served from a

Box 54.1. Diagnosis of Habits in Pediatric Patients

Childhood Habits

- History of a habit
- Callus on thumb or fingers
- Short, chewed nails
- Alopecia
- Lead intoxication
- Iron deficiency anemia
- Tooth surface loss
- Masticatory muscle hypertrophy

cup from birth develop no interest in sucking. Humans and other primates spend more time in nonnutritive than in nutritive sucking. Monkeys use a 5-point hold, with 2 hands, 2 feet, and mouth (holding on to their mother's nipple) for attachment. Universal thumb-sucking is noted even in orphan monkeys, and sucking is thought to be an important aspect of environmental adaptation. Nonnutritive sucking occurs even in the absence of fatigue, hunger, or discomfort and has a purpose in itself—to provide comfort and be self-soothing. The maximum intensity of sucking occurs at 7 months of age. For older children (≥3 years), sucking is also a way of coping with boredom.

In bottle-fed infants, thumb-sucking seems to commence when feeding stops. Some infants, described as "type A," seem to be satisfied only when their thumb is in their mouth. As infants spend more time engaged in motor activity, they spend less time thumb-sucking. Placid infants who cry less also do less sucking. Some studies have shown that thumb-sucking is less common in breastfed infants and that thumb-suckers as a group feed less frequently (every 4 hours rather than 3 and for 10 minutes rather than 20).

Nail-biting is related to thumb-sucking, a form of oral gratification, and children may progress from thumb-sucking to nail-biting. The pattern of nail-biting usually involves placement of the hand in the vicinity of the mouth, tapping of the fingers along the teeth, quick spasmodic bites with the fingers around the central incisors, and the removal and inspection of the hands. Other oral habits, such as pencil gnawing, gum chewing, lip biting, and nail picking, are related activities, as is nose picking. The cause of teeth grinding is unclear but may be related to malocclusion.

Rhythmic movements are kinesthetically pleasing and soothing and a means of autostimulation. The etiology of hairpulling is less apparent. The *DSM-5* defines trichotillomania as chronic hairpulling often associated with hair ingestion. In recent years, investigators have linked trichotillomania to disorders of serotonin reuptake and placed it in the category of obsessive-compulsive behavior. Some individuals who engage in trichotillomania have abnormal findings on head positron emission tomography. Although the etiology of trichotillomania is unclear, affected children share certain features, which have been characterized as fiddling SHEEP (sensation, hands, emotion, environment, perfectionism). The overriding factor is a need for tactile stimulation. Pica, which is also considered abnormal, may be associated with intellectual disability, environmental deprivation, or inadequate nutrition, particularly iron deficiency. It may also have a cultural basis. Geophagy (ie, ingesting earth substances such as clay) was related to the ingestion of kaolin, found in clay, in individuals of west African origin. Such clay had antidiarrheal properties and helped treat dysentery and other intestinal conditions. This practice persisted in Georgia, which, following the slave trade, had a large population of descendants from west Africa. Adolescents with pica may experience stress relief when they ingest certain nonfood products.

Differential Diagnosis

The differential diagnosis of most habits is not difficult. Tics or habit spasms should be differentiated from *Tourette syndrome*, which is a neurologic disorder, reported in 1 in 3,000 children, characterized by severe, frequent, and multiple tics (see Chapter 130). These tics are also often vocal and consist of sounds such as hissing, barking, grunting, or coprolalia (repeating profanities). Some rhythmic habits may be mistaken for seizures but can be easily distinguished because of the stereotypical, repetitive nature of the behavior.

Trichotillomania usually has a classic physical appearance that has been referred to as *tonsure* (*Friar Tuck*) pattern baldness, with baldness around the vertex of the head. Unilateral temporal baldness is also a consequence of trichotillomania. The differential diagnosis of trichotillomania includes alopecia areata, tinea capitis, syphilitic alopecia, and androgenic alopecia (see Chapter 136). Broken hairs of variable length usually characterize alopecia secondary to trichotillomania. Other disorders in the differential diagnosis include traction alopecia, related to tight braids or hair brushing; atopic eczema; seborrheic dermatitis; hypothyroidism; systemic lupus erythematosus; and dermatomyositis. When trichotillomania is associated with a trichobezoar and signs of gastric outlet obstruction, the differential diagnosis includes neuroblastoma, lymphoma, and gastric carcinoma.

Cutting is not a benign habit, but it can provide stress relief, a feature of many benign childhood habits. It is usually associated with a wide range of mental and behavioral health issues, including depression; anxiety; eating disorders, especially bulimia nervosa; a history of prior sexual abuse; and obsessive-compulsive symptoms. The mechanism by which cutting alleviates stress and anxiety has not been elucidated, but the role of endogenous endorphins has been suggested. Cutting is felt not to represent suicidal behavior, but some studies differentiate the site of cutting as predictive of suicidality: Wrist cutters, as opposed to arm cutters, have a higher rate of suicidal ideation and attempts. All cutters are at greater risk for suicide than the general population. Management generally involves referral to a mental health specialist and the use of psychotherapy. Other forms of self-injury are reported with increased frequency among children with developmental disabilities, including autism spectrum disorder (see Chapter 132).

Evaluation

History

Children who present with thumb-sucking, nail-biting, and teeth grinding usually do not require an assessment other than a routine health supervision history and physical examination. The history should determine the specific circumstances when the habit is manifest. Is the habit more likely to emerge when the child is tired or stressed? Habits must also be evaluated in the context of the child's developmental level and home situation. Understanding the effect of the habit on the child and family is important. Children who present with movements that resemble tics should be carefully questioned about the frequency and duration of the tics, the effect of the tics on their behavior, and whether coughing is associated with the tics (sign of Tourette syndrome).

The occurrence of obsessive-compulsive mannerisms should also be noted (Box 54.2).

Physical Examination

A routine physical examination should be performed. The physical examination may reveal the sequelae of the habit, such as thumb calluses, candidal infection of the nails, or evidence of malocclusion with an overbite (Figure 54.1). Children with suspected trichotillomania should undergo a thorough assessment of their scalp in an effort to differentiate other causes of alopecia (see Chapter 136). A careful neurologic examination should be performed in children with tics, and referral to a child neurologist may be indicated in children with suspected neurologic disorders.

Laboratory Studies

Routine laboratory studies are not needed in children diagnosed with common habit disorders. Studies are indicated if the children have experienced complications from the habit. For instance, if osteomyelitis is suspected in a nail-biting child, magnetic resonance imaging would be the study of choice.

Children with trichotillomania should be evaluated for the disorders listed previously. An easy evaluation process for trichotillomania involves shaving the hair in the middle of the area of baldness. The growth of these small hairs is uniform because children are unable to pull them out. Head shaving may not be acceptable, however, to the parent or child. Disorders such as syphilis and collagen vascular diseases can be ruled out using appropriate laboratory studies. Fungal infections can be differentiated by the use of appropriate cultures. A Wood light examination may reveal fluorescence noted with certain fungal infections.

Children who present with pica should be evaluated for the presence of iron deficiency anemia and lead poisoning. If the history involves geophagy, testing stool or blood for parasites may be warranted, especially if a complete blood cell count reveals eosinophilia.

Box 54.2. What to Ask

Childhood Habits

- What about your child's habit concerns you?
- Is your child experiencing any adverse consequences (eg, being teased at school) as a result of the habit?
- What have you done to discourage your child from engaging in the habit?
- Does the habit interfere with your child's routine activities?
- Can you identify stressors in your child's life?
- Is your child comforted by the habit?

Figure 54.1. Anterior open bite associated with thumb-sucking.

Management

In general, parents should be queried about what they have done to decrease their child's engagement in the habit. The management of childhood habits should be tailored to the specific habit and the associated symptoms. For older children, self-monitoring and relaxation training may be helpful as alternative means of coping with stress. The issue of thumb-sucking versus the use of pacifiers can be addressed by anticipatory guidance. Pacifiers, which were previously discouraged, are now believed to have some advantages over thumb-sucking. A report from the American Academy of Pediatrics noted a decrease in the incidence of sudden infant death syndrome in infants who used a pacifier. With pacifiers, the risk of dental disturbances is lower because the pacifiers are softer and are accompanied by a plastic shield that puts counter pressure on the teeth. Pacifiers are also detachable and cleanable.

Pacifiers can be lost, however. Parents should be advised not to attach a pacifier to the child's shirt with a string because of risk of strangulation. For children who are pacifier dependent and unable to go back to sleep if they lose their pacifier at night, multiple pacifiers can be placed in the crib to make finding one easier. For infants who desire pacifiers because they complete their feeding in less than 20 minutes, a nipple with a smaller hole can be used or the cap can be screwed on the bottle more tightly to prolong the time spent in nutritive sucking. Dental problems may develop when pacifiers are used upside down, all day long, or after the eruption of permanent dentition.

It is suggested that parents do not try to stop thumb-sucking behavior until children have reached the age of 4 years. Dental problems in late thumb-suckers include anterior open bite, increased horizontal overlap (protruding upper incisors), intruded and flared upper incisors, lingually flipped lower incisors, and warped alveolar ridge. When thumb-sucking persists to school age, tongue thrust is noted, as are articulation problems, specifically with consonants *s, t, d, n, z, l,* and *r.* The physician should reassure parents that children who stop sucking their thumbs prior to the eruption of the secondary dentition are not at risk for poor dentition.

Numerous devices have been proposed to help with the cessation of thumb-sucking, but reported success has been variable. The use of arm restraints, particularly at night, is not recommended and may result in rumination. Bitter paints seek to reduce thumb-sucking by subjecting children to a bitter, aversive taste. This medication consists of 49% toluene, 19% isopropyl alcohol, 18% butyl acetate,

11% ethyl cellulose, and 0.3% denatonium benzoate. A 3/4-oz bottle is toxic if ingested in its entirety. Application of aversive tasting chemicals are used less frequently. Nocturnal application is needed if children suck their thumbs during the night. The principle of retraining, in which thumb-sucking becomes a duty and children are required to suck all 10 fingers one at a time, has also been recommended. Some recommend that elastic bandages be put on the hand of nocturnal thumb-suckers. Problems associated with thumb-sucking include sore thumbs, calluses, and candidal infections. Dentists may fashion a reminder appliance, called a palatal crib or rake, making it difficult for children to suck their thumbs. Such devices are usually applied for a minimum of 3 months. A fixed appliance is preferable to a removable one, and treatment should be initiated in spring or summer when children are engaged in numerous physical activities. A number of dental devices are available commercially and online including TGuard and Hand Stopper or Thumb Sucking Handaid. They may consist of a plastic covering for the thumb and hand. This covering eliminates the pleasurable sensation created by the interaction of thumb, saliva, and mouth. Encouragement works better than nagging, as a rule, and a reward system is particularly useful in children who are 5 to 6 years of age. Parents may be referred to books such as *Thumbs Up, Brown Bear* and encouraged to talk to their children about how good it feels not to suck their thumbs. A star chart and diary are also useful. Sometimes, telling children something like, "Mommy would be so proud of you if you didn't suck your thumb now that you're such a big girl or a big boy," is effective. In addition, the pressure to stop thumb-sucking becomes greater during the school years. Children who suck their thumbs are regarded by their peers in first grade as less intelligent, less happy, less likable, and less desirable as friends. A Cochrane review showed that orthodontic appliances and psychological intervention, both positive and negative, were successful in stopping thumb-sucking both short- and long-term.

In children who suck their thumbs and twirl their hair at the same time, the hair twirling stops once the thumb-sucking ends. The phenomenon is referred to as *habit covariance*. Hairpulling in young children often seems to resolve spontaneously but is more problematic in adolescents and adults. Management of trichotillomania usually involves non-pharmacological treatments. In children, behavior modification, including putting socks on the hands and the use of time-out for hairpulling, in addition to extra attention for not pulling the hair, is recommended. Substituting behavior is also encouraged. For instance, children should be advised to sit on their hands, wear gloves, pull rubber bands, or squeeze a ball whenever they have an urge to pull their hair. In older individuals, hairpulling may be related to obsessive-compulsive disorders. A form of cognitive-behavioral therapy referred to as habit reversal therapy is said to have significant empirical support. This therapy involves an understanding of the hairpulling by the patient and then a combination of awareness training, self-monitoring, stimulus control, and competing response procedures. Habit reversal therapy is more appropriate for older children and adolescents. Trichotillomania may lead to the presence of trichobezoars (hair balls) from swallowed hair. Sometimes, hair balls can extend through the gastric outlet into the small intestine, a phenomenon referred to as Rapunzel syndrome. Gastric hair balls can be dissolved enzymatically or with the installation of a cola soda through a nasogastric tube. If such maneuvers fail, they are removed endoscopically or through surgery. Pharmacological therapy for trichotillomania is not routinely recommended for the management of affected children. In adults, selective serotonin reuptake inhibitors, clomipramine, bupropion, and risperidone have been used. There are currently several mobile apps that can be used to monitor behavior and assist with treatment strategies. Children whose symptoms have not improved with behavioral interventions should be referred to a mental health professional for additional management.

Nail-biting also often responds to behavior modification. As is sometimes used to stop thumb-sucking, denatonium benzoate, a bitter chemical compound, can be applied to nails, although results are variable. Olive oil may be put on the nails to make them soft so there are fewer jagged edges to bite. Habit reversal therapy is another recommended modality to reduce biting. The promise of a professional manicure may be an incentive for young girls to let their nails grow. Recently, smart watches, as well as other devices worn on the wrist, have been used to track hand movements and alert the individual to the biting. In the children's book, *The Berenstain Bears and the Bad Habit,* collecting pennies is suggested as a habit substitution for nail-biting.

Rhythmic habits are less easy to modify. For the most part, reassurance is all that is needed. The use of metronome-like devices has had no demonstrable effect. Children older than 3 years who disturb the family's sleep with their rhythmic habits may be given mild sedatives, such as diphenhydramine or hydroxyzine. Medications to reduce head banging include transdermal clonidine and thioridazine (eg, Mellaril). Other maneuvers involve placing the crib or bed on carpeting or bolting the crib to the wall to decrease the amount of noise from movement.

Children who engage in biting behavior should be managed with behavior modification, including praising of good behavior and time-out for inappropriate behavior. Aversive conditioning involves the placement of some unpalatable food, such as a lemon or onion on a necklace, and having the child bite on that object rather than biting another child. Biting behavior is reported to be extinguished with this technique. Another option is the placement of a whistle. The child blows the whistle rather than biting the other child.

Nose picking is a common habit in children and adults. One suggestion to extinguish or minimize this habit involves letting children look in a mirror and pick their nose or videotaping the child while nose picking. Their reaction is that nose picking looks "gross" and the habit may decrease in frequency. Keeping the nasal mucosa moist through the application of lubricant such as petroleum jelly will reduce the presence of dried material in the nose, which often provides the impetus to pick.

Iron deficiency related to pica requires iron supplementation. Lead intoxication should be managed with chelation and environmental manipulation. One strategy suggested to reduce pica is to create a "pica box." The individual puts substitute substances, such

as popcorn or chewing gum, in the box, and the substitute material is used to satisfy the urge to ingest the desired product.

Prognosis

Most habits are not harmful to children's health. The major problem is social acceptability. Parents should be encouraged to stop a habit before it becomes ingrained. This can often be done by praising good behavior and encouraging activities during which the unwanted behavior does not appear. Habits that do not respond to parental influence often resolve spontaneously under peer pressure.

CASE RESOLUTION

It is important for the physician and the mother to empower the boy to stop thumb-sucking before he finds himself ridiculed by his classmates. He might be allowed to suck his thumb at certain times and in certain places (eg, "You can suck in your room after school for 15 minutes"). Books geared at children and parents to help stop thumb-sucking are recommended, and the boy is rewarded for times when he is not sucking his thumb.

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CHAPTER 55

Enuresis

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CASE STUDY

A 9-year-old boy who is in good general health is evaluated for a history of bed-wetting. He is the product of a normal pregnancy and delivery, and he achieved his developmental milestones at the appropriate time. The boy was toilet trained by the age of 3 years, but he has never been dry at night for more than several days at a time. Bed-wetting occurs at least 3 to 4 times a week even if he is fluid restricted after 6:00 pm. The boy never wets himself during the day, has normal stools, and is an average student. His father had enuresis that resolved by the time he was 12 years old.

The boy's physical examination is entirely normal.

Questions

1. What conditions account for the symptoms of enuresis?
2. What is the appropriate evaluation of children with enuresis?
3. What is the relationship between enuresis and emotional stresses or psychosocial disorders?
4. What management plans are available for enuresis?
5. How do physicians decide which management technique is appropriate for which patients?

Enuresis is defined as involuntary or intentional urination in children whose age and development suggest achievement of bladder control. Voiding into the bed or clothing occurs repeatedly (at least twice a week for at least 3 consecutive months). On average, urinary continence is reached earlier in girls than in boys, and the diagnosis of enuresis is reserved for girls older than 5 years and boys older than 6 years. The term *diurnal enuresis,* wetting that occurs during the day, has been replaced by *daytime incontinence.* The International Children's Continence Society promotes a standardization for enuresis-related terminology. It prefers the use of the term *incontinence* to denote uncontrollable leakage of urine, intermittent or continuous, that occurs after continence should have been achieved. *Nocturnal* or *sleep enuresis* refers to involuntary urination or incontinence that occurs during the night. The term *primary nocturnal enuresis* is used when children have never achieved sustained dryness, and *secondary enuresis* is used when urinary incontinence recurs after 3 to 6 months of dryness. Monosymptomatic nocturnal enuresis means that nighttime wetting is the only symptom. Children who experience urgency, frequency, dribbling, or other symptoms have *polysymptomatic enuresis.* Such symptoms may be related to inappropriate muscle contraction, are often associated with constipation, and are termed *dysfunctional elimination syndrome* or *bowel/bladder dysfunction.*

Physicians can be particularly helpful by routinely questioning parents about bed-wetting during health supervision visits. Many families are otherwise reluctant to bring up this embarrassing concern because enuresis is viewed as socially unacceptable. It poses particular difficulties if children are invited to sleep away from home, such as at a slumber party. In addition, enuresis may be associated with other behavioral or developmental problems, such as attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression, that warrant inquiring about.

Epidemiology

Enuresis affects 5 to 7 million individuals in the United States. It is 1 of the most common conditions of childhood, affecting 10% to 20% of first-grade boys and 8% to 17% of first-grade girls. By age 10 years, 5% to 10% of boys still are enuretic (1% of US Army recruits are enuretic). Seventy-four percent of affected children have nocturnal enuresis, 10% daytime incontinence, and 16% both. Primary enuresis affects the majority (75%–80%) of children with enuresis, and 80% to 85% of these children have monosymptomatic nocturnal enuresis. Although the overall prevalence of secondary enuresis is lower (20%–25%), it increases with age; secondary enuresis makes up 50% of cases of enuresis in children 12 years of age.

Several epidemiological factors have been associated with enuresis, including low socioeconomic status, large family size, single-parent family, low birth weight, short height at 11 to 15 years of age, immature behavior, relatively low IQ, poor speech and coordination, and encopresis (fecal incontinence; 5%–15% of cases). Enuresis has been associated with obstructive sleep apnea, in which an increased level of atrial natriuretic factor has been reported. Atrial natriuretic factor inhibits the renin-angiotensin-aldosterone pathway, causing diuresis. Correcting obstructive sleep apnea with tonsillectomy or adenoidectomy can lead to the elimination of enuresis. Enuresis has a familial basis, with 44% being enuretic if 1 parent was enuretic and as many as 77% of children being enuretic if both parents were similarly affected. Concordance for enuresis is reported in up to 68% of monozygotic twins and between 36% and 48% of dizygotic twins.

Clinical Presentation

A history of enuresis may be obtained as a presenting symptom or elicited by physicians during a health supervision visit. Medical conditions such as encopresis, obstructive sleep apnea (nighttime snoring), or ADHD may be associated with enuresis (Box 55.1). Children with ADHD have a 30% greater risk of being enuretic compared with their peers who do not have ADHD. The physical examination is usually normal.

Pathophysiology

Delayed control of micturition has several possible causes (Box 55.2).

- Faulty toilet training may perpetuate diurnal and nocturnal enuresis but is not expected to selectively perpetuate the latter. Parental expectations are believed to play a role in the toilet-training experience. Parents who allow children to sleep in overnight diapers or pull-ups may delay the achievement of nighttime dryness, but it is unlikely that the use of diapers or pull-ups causes nocturnal enuresis. Poor toilet habits, particularly infrequent voiding or constipation, may be associated with urinary tract infections (UTIs) and account for secondary enuresis.
- Maturational delay. The development of the inhibitory reflex of voiding may be delayed in some children, which may contribute to enuresis until the age of 5 years. This is similar to the range in which children achieve other developmental milestones. It is unlikely that maturational delay persists as a cause of enuresis beyond this age. Experts believe that maturational delay is not a reasonable explanation if children can achieve dryness in the daytime but not at night.
- Small bladder capacity. Evidence suggests that some children with enuresis have smaller than normal bladder capacities. Bladder capacity in ounces is estimated as the age in years plus 2. For example, 5-year-olds have a bladder capacity of 7 oz (210 mL). Adult bladder capacity is 12 to 16 oz (360–480 mL). Small bladder capacity is associated with diurnal frequency or incontinence.
- Sleep disorder/impaired arousal. The relationship between enuresis and sleep has been the focus of numerous studies, some with conflicting results. It has been suggested that children with enuresis are in "deep sleep" and do not sense a full bladder. This is often the parent's perception of their child's sleep pattern. However, studies have shown that enuresis occurs during all stages of sleep, particularly in the first one-third of sleep and in transition from non-rapid eye movement (non-REM) stage 4 to rapid eye movement (REM) sleep. During this period, body tone, respiratory rate, and heart rate increase, and erection and micturition occur. Studies suggest that the arousal center in the brain fails to respond (ie, the child does not awake) to full bladder sensation. Children with enuresis do not seem to sleep more deeply than other children. However, children with enuresis may have diminished arousal during sleep. In one study, 40% of children with enuresis, compared with only 8.5% of children without enuresis, did not awaken to an 80-dB noise. Other studies highlight the association of nocturnal enuresis with fragmented sleep, a lower proportion of motionless sleep, and more nighttime awakenings.

  Recent studies suggest a correlation between nocturnal enuresis and periodic limb movement disorder. This disorder consists of involuntary movement of the lower extremities (ie, knee, hip, or ankle) during non-REM sleep. Periodic limb movement disorder is related to dopamine-depletion, leading to the disinhibition of spinal-cord motor and sensory reflexes. Dopamine deficit may affect the micturition center in the brain, leading to increased bladder contractions; hence, the association with enuresis.
- Allergens. No evidence confirms the notion that exposure to certain foods (eg, food additives, sugar) contributes to enuresis. However, some parents believe that bed-wetting is decreased if certain foods, such as sodas and sweets, are eliminated from the diet. The ingestion of caffeine-containing beverages may exacerbate nocturnal enuresis through the diuretic effect of caffeine.
- Nocturnal polyuria/relative vasopressin deficiency. Research has shown that although children who do not have enuresis exhibit a diurnal variation in arginine vasopressin (AVP) secretion, this rhythm is disturbed in some children with enuresis, resulting in

Box 55.1. Diagnosis of Enuresis in Pediatric Patients

Enuresis

- Bed-wetting
- Wet underwear
- Old enough to be toilet trained
- Bowel and bladder dysfunction
- Precipitating problem, such as diabetes or urinary tract infection
- Encopresis
- Attention-deficit/hyperactivity disorder
- Family history of enuresis

Box 55.2. Causes of Enuresis

Primary Enuresis

- Faulty toilet training
- Maturational delay
- Small bladder capacity
- Sleep disorder/impaired arousal
- Allergens
- Nocturnal polyuria/relative vasopressin deficiency
- Dysfunctional bladder contraction

Secondary Enuresis

- Urinary tract infection
- Diabetes mellitus
- Diabetes insipidus
- Nocturnal seizures
- Genitourinary anomalies
- Sickle cell anemia
- Medication use
- Emotional stress

nocturnal polyuria. In addition to regulating urine formation, AVP also regulates circadian rhythm. Dysregulation of AVP can, therefore, be associated with nocturnal polyuria as well as disturbed sleep.

- Dysfunctional bladder contraction. In cases of daytime incontinence, contractile disturbances of the bladder affect normal voiding. Children with an "uninhibited bladder" have not learned to inhibit bladder contraction. They may assume a certain posture, called Vincent curtsy, in an effort to prevent micturition. Some children exhibit uncoordinated, incomplete voiding and the urine exits the urethra in a staccato stream. Trabeculations or bladder wall thickening may be noted on imaging studies.

  Daytime incontinence can be related to problems with bladder filling and storage or to bladder emptying. Each of these functions is under different neurologic control, with filling and storage under the sympathetic nervous system and bladder emptying related to the action of acetylcholine and the parasympathetic system. Effective voiding requires the coordinated effort of these 2 phases. Management of daytime incontinence is dependent on which phase is malfunctioning.

Differential Diagnosis

The differential diagnoses for both primary and secondary nocturnal enuresis are noted in Box 55.1. A specific organic problem is rarely the cause of primary nocturnal enuresis, although abnormal AVP regulation may affect some children. However, secondary enuresis may result from an organic problem, such as UTI, diabetes mellitus, diabetes insipidus, nocturnal seizures, genitourinary anomalies (eg, ectopic ureter), sickle cell anemia, medication use (eg, diuretics, theophylline, lithium), or emotional stress. When primary enuresis is diurnal and nocturnal, some of these conditions should be considered. Additional diagnoses include neurogenic bladder, which may occur in association with cerebral palsy; sacral agenesis; and myelomeningocele. Some children experience urinary frequency, a benign self-limited condition characterized by the sudden need to urinate very frequently, often 25 to 30 times a day. The condition occurs most often in children between 3 and 8 years of age, is self-limited, and is felt to be stress related. A urinary diary, noting time and amount of voiding, is sometimes helpful in diagnosing the condition.

Evaluation

History

A thorough history should be obtained when evaluating children with enuresis (Box 55.3). It may be helpful for the child or family to keep a diary recording the episodes of nocturnal enuresis over several weeks to a month. It may be useful to note the time the child ate dinner, what was eaten, and the time the child went to bed to help determine if there is any discernible pattern or contributing environmental factors.

Physical Examination

A general physical examination should be performed, with particular attention to certain areas. The pattern of growth should be plotted. Blood pressure should be obtained. The abdomen should be assessed for evidence of organomegaly, bladder size, and fecal impaction. An anal examination should be performed to evaluate rectal tone.

If possible, physicians should watch children void. Practitioners should determine whether children can start and stop micturition and whether the stream is forceful. Dribbling in girls may indicate an ectopic ureter. A more sophisticated approach involves the uroflow test, in which the patient voids into an apparatus that electrically senses the rate of flow. A graph is generated that notes the flow rate and quantity. This study is most useful in children with diurnal incontinence. The appearance of the genitalia should be assessed. A rash in the genital area may be secondary to wetness from urinary incontinence. The skin may be macerated, erythematous, or hyperpigmented secondary to persistent moisture and irritation.

Labial fusion in girls may trap urine, allow reflux into the vagina, and lead to dribbling. Meatal stenosis, epispadias, hypospadias, or cryptorchidism may be present in boys. Any of these conditions is suggestive of a possible underlying genitourinary anomaly.

Neuromuscular integrity of the lower extremities should be evaluated. This may provide a clue to a disorder such as spina bifida occulta. The presence of some anomaly in the sacral area, such as a sacral dimple or a tuft of hair, may also be a sign of this condition.

Box 55.3. What to Ask

Enuresis

- Is the enuresis primary or secondary?
- Is the enuresis diurnal, nocturnal, or both?
- How old was the child when toilet training occurred?
- How old was the child when daytime and nighttime dryness was achieved?
- How often does the child urinate and defecate during the average day?
- Is the child's urinary stream forceful or dribbling?
- Does the child dribble before or after voiding?
- Does the child experience symptoms such as polydipsia, polyuria, dysuria, urgency, frequency, or problems with passing stool?
- Who changes the bed and who washes the bedclothes after bedwetting occurs?
- Does the child wear diapers or pull-ups or use incontinence pads overnight?
- Does the child seem to delay using the toilet?
- Does the child assume any unusual or distinct postures to avoid being incontinent?
- What is the attitude of the family toward the child with enuresis? Are family members accepting or ashamed?
- Has the family tried any treatments yet?
- Is there a family history of enuresis?
- Does the child have other symptoms, such as encopresis, attention-deficit/hyperactivity disorder, or obstructive sleep apnea?

Laboratory Tests

Usually the diagnosis of nocturnal enuresis is determined by the history. Only a minimal laboratory evaluation is indicated in most children with primary enuresis. Urinalysis, including specific gravity, is usually indicated. A complete blood cell count, serum electrolytes, and blood urea nitrogen should also be considered. Studies such as urine culture and blood glucose are more often indicated in cases of secondary enuresis.

Some studies suggest that AVP levels be assessed, although this is challenging because of the instability of the molecule and the short half-life (20 minutes). In addition, more than 90% of AVP is bound to platelets. There is a biomarker for AVP, which is a precursor peptide, copeptin. Copeptin has been used to differentiate central diabetes insipidus from nephrogenic diabetes insipidus and, in a single study to date, helped differentiate those with severe bedwetting from those with milder enuresis. The role in the routine evaluation of children with nocturnal enuresis is yet to be defined.

Imaging Studies

In cases in which urinalysis is abnormal, the culture is positive, or genitourinary anomalies are apparent on physical examination, renal ultrasonography and voiding cystourethrography may be warranted. Vertebral radiography or magnetic resonance imaging is appropriate in the diagnosis of spina bifida. Magnetic resonance urography is helpful in girls suspected of having an ectopic ureter. Electroencephalography is indicated if nocturnal epilepsy is suspected. Urodynamic studies to evaluate bladder contractility are controversial but are recommended by some urologists in children who do not respond to traditional therapy or are suspected of having spina bifida occulta not revealed on other studies.

Management

Primary Enuresis

Family counseling about enuresis should be part of all management plans. Issues related to psychosocial stress should be explored, particularly in cases of secondary enuresis. Families should be advised that the wetting is not intentional and that punishing children for accidents is inappropriate. However, children should be given the opportunity to help by removing soiled bedding or helping with the laundry. Limiting fluids and caffeinated beverages in the evening and having children void before bedtime are recommended steps. Children should be rewarded for dry nights. Star charts, in which a sticker or gold star is applied to a calendar for each dry night, have traditionally been used. Star charts and rewards are part of motivational therapy, which is a recommended first-line intervention for younger children (5- to 7-year-olds) who do not wet the bed every night. Success, as defined by a 2-week period of dry nights, occurs in 25%, and improvement is reported in more than 70%. The exclusive use of these charts without other interventions, however, has limited success and suggests that the enuresis may have a volitional component. Star charts should be used in conjunction with other management strategies.

Two treatment modalities are acceptable for managing enuresis. Most studies do not support the use of fluid restriction as a reliable isolated means of controlling enuresis. Some children benefit from sequential or combination therapy.

Conditioning therapy involves the use of an alarm that is triggered when children void during the night. Children are awakened by the sounding of the alarm, and further urination is inhibited. Eventually, bladder distention is associated with inhibition of the urge to urinate. When conditioning therapy is used for 4 to 6 months, it is associated with a success rate of 70%. If the alarm is used for 4 more weeks with sustained dryness, relapses are uncommon.

Because patient cooperation is needed with the alarm system, its use is reserved for children age 7 years and older. There are multiple different types of alarm systems, including wireless alarms, wearable alarms, and pad-type alarms. For example, 1 system involves a transistor device that contains a small sensor in the underwear and an alarm on the wrist or collar. Some of these alarms are watches that resemble devices for measuring steps or heart rate. Most systems now use vibrations so other family members are not disturbed by loud alarms.

Overall, conditioning devices have a cure rate of 70% to 85% and a relapse rate of 10% to 15%. They incur a one-time cost of $50 to $75, although some of the newer systems may cost up to $200. Conditioning devices may be covered by insurance companies if the alarm is prescribed by a physician as a medical device. Approximately 30% of families discontinue use of the alarm before the recommended period for various reasons. Conditioning without the use of auxiliary alarms may also be undertaken. One proposed method involves instituting a self-awakening program. Older school-age children practice lying in bed during the daytime and simulating the experience of awaking, sensing a full bladder, and going to the toilet. Another dry-bed training program involves parents awaking their children first hourly and then at longer intervals over the period of about 1 week. Children eventually learn to self-awake. A 92% success rate with a relapse rate of 20% is reported with this program.

Transcutaneous electrical neural stimulation therapy, which has been used successfully in patients with hyperactive bladder and polysymptomatic enuresis, has been tried in patients with monosymptomatic enuresis with some success, but the results are preliminary.

Pharmacological agents include tricyclic antidepressants and desmopressin. Generally, medications produce a more rapid response but have a higher rate of relapse. Tricyclic antidepressants, especially imipramine, have been successfully used to treat nocturnal enuresis, although the mechanism of action is uncertain. The antidepressant action of the drug, its effect on sleep and arousal, and its anticholinergic properties may all play a role. There is also some evidence that imipramine increases concentrations of antidiuretic hormone. Imipramine may also act partially by reducing clearance of solutes and partially by increasing urea and water

reabsorption from the kidneys. The bladder capacity of individuals with enuresis treated with imipramine may be increased by 34%, which indicates that the anticholinergic effects of the drug may be the most significant.

Imipramine should not be prescribed for children younger than 6 or 7 years because of potential adverse effects. The recommended dosage is 0.9 to 1.5 mg/kg/day. In general, children younger than 8 years are given 25 mg 1 to 2 hours before bedtime, and older children are given 50 to 75 mg. Beneficial results usually occur within the first few weeks of therapy. Medication is usually continued for 3 to 6 months to prevent relapses, which are reported in up to 75% of cases. The drug should be tapered by reducing the dose or using an alternate-night regimen. Side effects are rare and include insomnia, nightmares, and personality changes. Acute overdoses are potentially fatal secondary to cardiac complications. The initial cure rate is 10% to 60% with a relapse rate of 90%. The monthly cost of imipramine is about $25 to $30. Because of the potential cardiotoxicity, reboxetine, a newer antidepressant, has been used with equal benefit, although the cost may be higher.

Desmopressin, an analog of vasopressin, the antidiuretic hormone, is another pharmacological agent used for enuresis. Desmopressin most likely works by decreasing nocturnal urine production. Most patients who respond to desmopressin have a large bladder capacity, large overnight urine volume, and low urine osmolarity overnight. These patients respond rapidly to desmopressin and become dry within 1 to 2 weeks of the initiation of therapy. The medication is taken orally as a 0.2-mg tablet 1 hour before bedtime. The dose may be increased by 1 tablet at weekly intervals (maximum dose: 0.6 mg). Desmopressin in nasal spray is no longer recommended for the treatment of enuresis because of the risk of severe hyponatremia, seizures, and even death. Hyponatremia has also been reported with oral desmopressin in the setting of high fluid intake sometimes associated with habit polydipsia. Fluid restriction is recommended from 1 hour before until 8 hours after desmopressin administration. While some physicians recommend a 6-month course of the medication, others suggest a shorter trial period. If patients achieve a 2-week period of dryness, the dose can be tapered at 2-week intervals. The cure rate is 40% to 50% with a relapse rate of 90% off medication. There is a biomarker, aquaporin 2, that can assess for clinical effectiveness. The cost of desmopressin is less than when initially recommended, ranging from $30 to $50 a month, although some insurers may require prior authorization for its use.

Some children do not respond to desmopressin. They tend to have small bladder capacity, low overnight urine volume, and high urine solute load. These patients frequently have comorbidities that require management. In other nonresponders, excessive prostaglandin production has been noted, and some of these patients will respond to nonsteroidal anti-inflammatory drugs.

Oxybutynin is an antispasmodic, anticholinergic agent used in the management of daytime incontinence or polysymptomatic nocturnal enuresis. The dosage is 5 mg at bedtime for children 6 to 12 years of age and 10 mg at bedtime for children older than 12 years. The response rate is 33%, and the major side effects include drowsiness, flushing, dry mouth, constipation, and hyperthermia. Hyoscyamine sulfate and flavoxate hydrochloride are 2 other medications used for daytime incontinence.

Treatment of enuresis in children with small bladder capacities includes bladder retention training. Such children are fluid loaded and asked to delay voiding for 5 to 10 minutes. This strategy is generally reserved for children with daytime incontinence.

Associated symptoms, particularly constipation and encopresis, should be adequately addressed.

Secondary Enuresis

The management of secondary enuresis should focus on the treatment of the causal disorder, such as a UTI or diabetes mellitus.

Prognosis

The prognosis for children with enuresis is good. The spontaneous cure rate is 15% per year overall, although those with severe bed-wetting (ie, 5 wet nights per week) have only a 50% chance of achieving spontaneous remission before adulthood. Medical management results in a reduction in symptoms in more than 70% of affected children.

CASE RESOLUTION

The boy has primary nocturnal enuresis. The history of childhood enuresis in the father is significant. Two management options, behavior modification and treatment with desmopressin or imipramine, can be discussed with the family. The child's symptoms will probably spontaneously improve over time.

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CHAPTER 56

Encopresis

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CASE STUDY

A 7-year-old boy is seen with a report of soiling his underpants. His mother states that he has never been completely toilet trained and that stool-related accidents occur at least 2 to 3 times a week, mainly during the day. The boy rarely has a spontaneous bowel movement without assistance. He sits on the toilet for just a few minutes and passes small, pellet-like stools. His mother has not previously sought medical care for this problem.

The boy is quite fidgety during the physical examination. His vital signs are normal, and his height and weight are at the 25th percentile. His abdomen is soft but distended, with palpable loops of stool-filled bowel. A small amount of stool is present around the anus and in the boy's underpants. Digital examination of the rectum reveals hard stool. The rectal tone is normal, as is the rest of the physical examination.

Questions

1. What is the definition of encopresis?
2. What is the difference between retentive and nonretentive encopresis?
3. What are some physiologic conditions that contribute to encopresis?
4. What conditions may be mistaken for encopresis?

Encopresis is the voluntary or involuntary repeated passage of stool into inappropriate places (eg, clothing) in children who, based on their age, should be toilet trained (usually at least 4 years of age, the age at which 95% of children have achieved stool continence) and who exhibit a normal developmental level and who have no primary organic pathology. One such encopretic event occurs each month for at least 3 months. The term encopresis, which was coined in 1926 by Weissenberg and originally was used for children with psychogenic soiling, is similar to *enuresis* (ie, urinary incontinence). Unlike enuresis, however, encopresis rarely occurs at night. Currently, "encopresis" is used in a broader sense to refer to all types of fecal incontinence. "Functional fecal incontinence" is the currently preferred term as recommended by the Multinational Working Teams to Develop Diagnostic Criteria for Functional Gastrointestinal Disorders.

Retentive encopresis, also referred to as *functional fecal retention with encopresis* or *retentive fecal incontinence*, occurs in the setting of functional constipation (ie, obstipation), in which chronic rectal distention results in the seepage of liquid stool around hard, retained feces. Sometimes this is called "overflow," "fecal soiling," or "pseudoincontinence," because the individual has the potential for bowel control. Onset of symptoms is usually approximately 4 years of age. Between 80% and 95% of cases of fecal incontinence are retentive. *Nonretentive fecal incontinence* is characterized by the passage of soft stool without colonic distention or retention of stool. Fecal incontinence in the absence of constipation is reported in up to 20% of children with encopresis. There are 2 categories of children with nonretentive fecal incontinence: those who can control defecation but who pass stool in inappropriate places and those who have true failure to achieve bowel control. *Primary encopresis* occurs when a child has never been completely toilet trained. *Secondary encopresis* occurs in a child who has had a period of complete continence of stool. Most children with encopresis have the secondary form.

Epidemiology

Encopresis is reported in approximately 1.5% of school-age children, and boys are affected 2 to 6 times more often than girls. This sex ratio reverses in the elderly, in which the prevalence of fecal incontinence is twice as high in females as in males. An association between encopresis, enuresis, attention-deficit/hyperactivity disorder, and autism spectrum disorder is sometimes present. Approximately 15% of children with enuresis also have encopresis. Family history for encopresis may also be positive; 16% of affected children have 1 affected parent (usually the father). An association between encopresis and child sexual abuse has been reported in a small number of children. No reported relationship exists between socioeconomic status, parental age, child's birth order, or family size.

Clinical Presentation

Children with encopresis have a history of staining of the underpants, which may be hidden in drawers or under beds by embarrassed children. Occasionally, parents are unaware of the problem. Stool incontinence occurs more frequently at home than in school. Some children have a history of constipation. Other children may be initially misdiagnosed as having diarrhea and are inappropriately placed on antidiarrheal medications, which exacerbate their problem. Parents may complain that their child exudes a fecal odor, but children are unaware they are malodorous (Box 56.1).

Approximately one-half of children with encopresis report abdominal pain, which may be vague and nonspecific or severe and crampy. Approximately 30% to 35% experience urinary incontinence or have a history of urinary tract infections (UTIs).

Pathophysiology

The 3 identified milestones at which a child may be at risk for the development of functional constipation are the introduction of dietary solids into an infant's diet, toilet training, and the start of school. Other factors that may precipitate secondary encopresis include change in schedule (eg, overnight school trips with use of communal bathrooms) and parental separation. Constipation, if associated with painful defecation, may contribute to the manifestation of retentive fecal incontinence. With time, the colon distends and liquid feces seeps around impacted stool (Figure 56.1). In 30% to 50% of children anal spasm (ie, anismus) occurs, and contraction rather than relaxation occurs during evacuation of feces. In another 40% of children, rectal hyposensitivity is apparent, resulting in unawareness of the presence of stool. Some children have an evacuation release disorder in which the presence of stool does not result in relaxation and stool evacuation. In such cases, the rectum is chronically distended by stool, water is absorbed, and stool becomes harder and drier. The distended rectum cannot sense the presence of the stool. When evacuation is attempted, the process is painful, resulting in further retention (see Chapter 124).

Encopresis has been associated with a short attention span and a high level of motor activity. Affected children are unable to sit on a toilet for more than a few minutes and do not adequately attend to the task of stool evacuation. As a result, they get off the toilet after the incomplete evacuation of only small amounts of stool. In some toddlers, constipation is related to the struggle of toilet training and an unwillingness to sit on the toilet (see Chapter 48).

Box 56.1. Diagnosis of Encopresis

- Incontinence of stool
- Urinary incontinence
- Constipation
- Hyperactivity
- Distended abdomen
- Stool-filled loops of bowel
- Lax rectal tone
- Soiled clothing or bedding
- Fecal odor

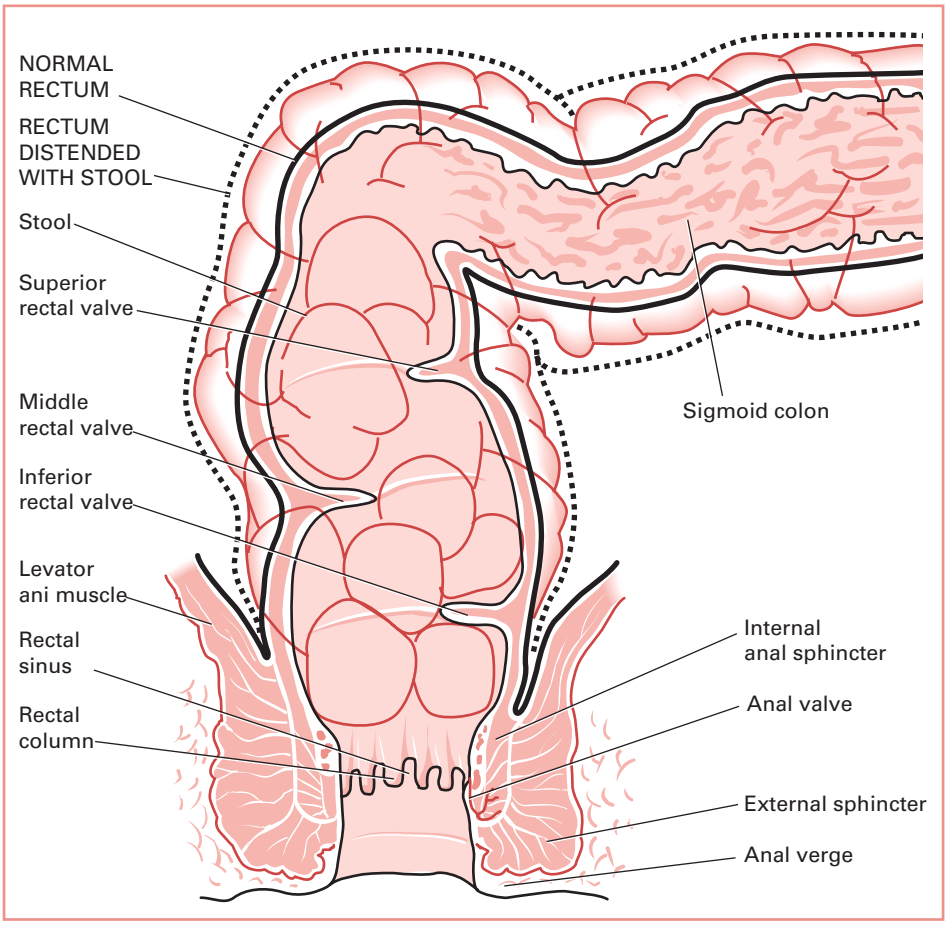

Figure 56.1. Diagram of the rectum, anal canal, and sigmoid colon distended with stool.

The etiology of nonretentive encopresis is unclear; however, 40% of children with nonretentive encopresis have never been adequately toilet trained. Comorbid psychiatric disorders as well as a history of sexual abuse have also been reported. Some children who have been chronically sexually abused have lax anal tone, which may contribute to fecal incontinence. A small proportion of children with nonretentive encopresis have a history of prior surgery in the rectosigmoid colon for the management of conditions such as congenital megacolon (ie, Hirschsprung disease) and imperforate anus. The child with acute proctitis secondary to cow milk protein allergy or inflammatory bowel disease may experience fecal incontinence; in this setting often the stool is also blood-tinged.

Differential Diagnosis

The differential diagnosis of encopresis focuses on organic conditions associated with chronic constipation. Organic conditions, which account for 5% to 10% of fecal incontinence, include congenital megacolon (ie, Hirschsprung disease), disorders of intestinal motility (eg, pseudo-obstruction), disorders of anal tone and anal anatomy (eg, imperforate anus with fistula), disorders of the lumbosacral spine (eg, meningomyelocele), previous surgeries (eg, repair of imperforate anus) and neurologic disorders (eg, intellectual and developmental disabilities, hypotonia). Neurofibromatosis, lead poisoning, and hypothyroidism are also associated with constipation. Congenital anorectal anomalies, which occur in 1 in 5,000 live births, are rare.

Most of these conditions can be ruled out on the basis of a careful history and physical examination. In some cases, specific testing, such as anal manometry or rectal biopsy, may be necessary to exclude a particular disorder.

Box 56.2. What to Ask

Encopresis

- At what age was the child toilet trained?
- Does the child have spontaneous bowel movements (without enemas or suppositories)? If so, how frequently?
- Does the child have large, dry, hard stools that clog the toilet?
- Does the child pass blood with the stool?
- Did the child pass meconium within the first 24 hours after birth?
- Has the child had any surgery in the anogenital area, spine, or bowel?
- Is the child taking any medication that can promote constipation, such as aspirin, iron, methylphenidate hydrochloride, imipramine, calcium channel blocking agent, or an anticholinergic agent?
- Does the child seem to resist the urge to defecate (eg, squeezes legs together and rocks back and forth)?
- Does the child have a history of enuresis or attention-deficit/hyperactivity disorder?
- What is the pattern of encopresis (ie, is the encopresis primary or secondary)?
- When and where does the child soil (eg, nocturnal, at home)?
- Have changes or stresses occurred in the home or family?
- What happens to the child's stained underwear?
- What has the family done to manage the problem?
- What is the child's diet? How much milk does the child drink? Does the child eat fruits and vegetables?

Evaluation

History

The physician should determine the age of onset of fecal incontinence as well as the age of initiation of toilet training. Generally, affected children are 4 years of age or older. A detailed history of the stool pattern should be obtained as well as a dietary history (Box 56.2). The frequency, consistency, and quantity of stools should also be noted. Additionally, the presence of nocturnal episodes of fecal incontinence should be determined. In cases of secondary encopresis, the duration of prior fecal continence and the occurrence of any events (eg, birth of a sibling, start of school) that may have precipitated the episodes of encopresis should be noted. Some children experience the onset of encopresis when they start school. Because of "toilet phobia," they are unwilling to use the public toilet in the school setting. It is important to note that not all children who experience constipation develop encopresis.

Physical Examination

A comprehensive physical examination is necessary, paying particular attention to the abdomen to check for the presence of distended, stool-filled loops of bowel. Fifty percent of children with retentive encopresis have a palpable fecal mass. The rectal area should be assessed for rectal tone, anal wink, and the presence of hard stool (which may be noted in up to 90% of children with encopresis). To elicit an anal wink, the skin adjacent to the anus should be stroked using a cotton swab. Some children with retentive encopresis may forcibly tighten their anal sphincter and their buttocks in response to a digital examination or because they are frequently contracting their external anal sphincter to prevent the seepage of liquid stool.

The child with a patulous anus may have a neurologic disorder and should undergo a thorough neurologic examination. Rectal prolapse, if present, may be indicative of chronic constipation or another condition (eg, cystic fibrosis). Perianal fissures may reflect passage of large, hard stools. Hemorrhoids are unusual in children and can be indicative of chronic constipation. Location of the anus should also be noted; anterior displacement may be suggestive of an incomplete type of imperforate anus.

Dysmorphic features should be noted; these may be suggestive of a syndrome of which constipation is a feature. Abnormalities around the anus, such as fistulas, should also be noted. Fistulas are found in Crohn disease. The underpants should be evaluated for the presence of stool, mucus, or pus. A sensory and motor examination of the lower extremities helps determine if any signs of spinal cord dysfunction are evident. An evaluation of the skin over the spinal area may reveal abnormalities, such as sacral dimples or tufts of hair.

The child who does not exhibit abdominal distention may have soft stool on rectal examination, which is indicative of nonretentive encopresis. Patulous anal tone is suspicious for spinal cord abnormalities or prior child sexual abuse.

Laboratory Tests

Most children with encopresis require few laboratory studies. Studies are selected with a focus on eliminating organic causes of encopresis, such as congenital megacolon (Hirschsprung disease) or spinal cord anomalies. Urinalysis and urine culture are recommended in children with fecal impactions to exclude UTI. Encopresis is reported to be an independent risk factor for UTI. Thyroid function studies, a lead level, celiac serology, and electrolytes, including serum calcium, have been suggested, particularly in children with refractory constipation. Anorectal manometry, which may be used to measure the pressure generated by the anal sphincter, may also reveal abnormalities of anal tone or evidence of aganglionosis. Manometry may also detect dyssynergic defecation characterized by failure of the muscle of the pelvis floor to relax during defecation. The Child Behavior Checklist is useful to determine if certain behavior problems exist. Such problems may potentiate the encopresis or result from it.

Imaging Studies

In most children with encopresis, imaging studies are not necessary. Abdominal radiographs obtained from children with retentive encopresis may reveal a distended, stool-filled bowel. In children with suspected nonretentive encopresis, abdominal radiographs can confirm the absence of constipation. A contrast enema with barium or a hydrosoluble substance is useful if congenital megacolon (Hirschsprung disease) or an anorectal malformation is suspected. Strictures, which may occur after necrotizing enterocolitis, are also detected on such radiographs. Electromyography to determine whether the innervation of the external anal sphincter is intact is recommended for the child with encopresis who does not respond to routine treatment.

Management

The management of encopresis is focused on patient and parent education and counseling with the goal of eventual complete rectal evacuation of stool. Typically, it takes 2 to 6 months to regain muscle tone of the anal canal. The child with anorectal malformations or prior gastrointestinal tract surgery may require additional surgical procedures to help them achieve fecal continence.

Rectal evacuation inevitably requires pharmacologic management to ensure an adequate cleaning out of retained stools. The decision about which laxatives to use depends on the severity of constipation. Polyethylene glycol 3350 has a very high success rate in the management of constipation and encopresis and in recent years has become the mainstay of therapy. The medication comes as a powder; generally, 17 g (0.6 oz) is added to juice or water. The medication may be given twice a day if there is no initial response. Other modalities include a high-fiber diet and stool-bulking agents or oral laxatives, such as senna derivatives, bisacodyl, or lactulose syrup, which may be used in association with stool softeners or lubricants (eg, mineral oil). Use of mineral oil has decreased. The amount of mineral oil may be titrated up to ensure success. Some physicians recommend that mineral oil be given until it oozes from the rectum, after which the amount may be titrated back to a lower level. Magnesium sulfate is also recommended to relieve constipation. Magnesium citrate can be used but should be administered cautiously and with the admonition to drink plenty of fluids to prevent dehydration. If the degree of retention is more severe, suppositories or enemas may be necessary. Occasionally, manual disimpaction is required. Alternative methods to manual disimpaction include 2 to 3 sodium phosphate enemas over 1 to 2 days or 226.8 g (8 oz) of mineral oil a day for 4 days. Pulsed irrigation–enhanced evacuation involves the insertion of a rectal tube and the installation of pulses of warm irrigating solution, simultaneously draining rectal contents. If these modalities are unsuccessful, it may be necessary to admit the child to the hospital for oral administration or nasogastric lavage using polyethylene glycol-electrolyte solution at 30 to 40 mL/kg/hour until successful evacuation has occurred. This procedure requires insertion of a nasogastric tube and 6 to 8 hours of treatment. After the fecal accumulation has been relieved, every effort should be made to keep the child regular. This can be accomplished with the combined use of toilet retraining, stool softeners or laxatives, and enemas or suppositories. Prokinetic agents, such as metoclopramide hydrochloride, may also be used.

Dietary manipulation is important to ensure sustained regular passage of stool. Parents should be advised that children require a high-fiber diet with fruit juices (eg, pear, peach) and decreased milk consumption (<16 oz/day). It has been suggested that a "team and coach" approach is the most successful route and that bowel training be likened to fitness training.

The toilet retraining process, or "enhanced toilet training," requires that the child sit on the toilet at least 2 or 3 times a day, usually after meals, for approximately 10 minutes or until the child has had a bowel movement. Some physicians recommend the use of an egg timer to ensure that the child spends the appropriate amount of time on the toilet. Some children are more receptive to time on a toilet if they have access to video games or shows during their time on the toilet. Children should be requested to maintain a diary of their evacuation, which may take the form of a star chart. Stars or other rewards are given for successful bowel movements in the toilet.

If a child skips a day between bowel movements, a suppository may be used (eg, glycerin, bisacodyl). If after administration of the suppository the child still has not had a bowel movement, an enema may be appropriate. This sequence should be maintained until the child is having bowel movements in the toilet and is not soiling for at least 1 month. Generally, it is necessary to use stool softeners for at least 3 to 6 months. It may be necessary to modify the regimen, particularly in younger children.

Behavior modification and biofeedback, such as using external anal sphincter electromyography, are 2 other modalities that can be used to help manage encopresis. Consultation with a specialist, such as a pediatric gastroenterologist, may be required.

Thirty percent of children with encopresis may need psychologic consultation. Psychologic intervention in the form of interactive parent-child family guidance has been successful when standard gastroenterologic intervention has failed. The child with evidence of child sexual abuse or nonretentive encopresis should be referred to a psychologist early in the course of therapy. The underlying psychosocial problems of the child with nonretentive encopresis must be adequately addressed before the condition can improve.

Prognosis

The prognosis for the child with retentive encopresis is reportedly good with appropriate intervention. In 1 study, children who were able to defecate a rectal balloon filled with 100 mL of water within 5 minutes were twice as likely as those who could not do so to recover from constipation and encopresis. It is estimated that approximately 30% to 50% of affected children experience long-lasting remission after 1 year, and up to 75% of affected children are in remission by 5 years.

The prognosis for the child with nonretentive encopresis is less predictable and is highly dependent on the underlying psychopathology.

CASE RESOLUTION

The boy exhibits typical manifestations of retentive encopresis. His condition should be managed with the use of laxatives, stool softeners, and toilet retraining with a star chart. The possible diagnosis of attention-deficit/hyperactivity disorder should be addressed separately but may be contributing to his inability to attend to the task of toileting.

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PART 4

Adolescent Health

CHAPTER 57

Culturally Competent Care for Diverse Populations: Sexual Orientation and Gender Expression

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CASE STUDY

The mother of an 11-year-old boy makes an appointment with you to discuss her son's "behavior problems." He is the youngest of 4 children and is doing well in fifth grade, but she is concerned that her son does not like typical "male" activities. He dropped out of Little League, will not join other sports teams, and prefers riding his bike by himself. Additionally, he still likes dressing up in costumes and prefers playing with girls rather than boys. His mother finally mentions that she is worried that her son will be gay and is wondering what she can do to help him develop "normally."

Questions

1. What is meant by gender expression, sexual orientation, and gender identity?
2. What is the role of the pediatrician in counseling parents and patients about gender expression, sexual orientation, and gender identity?
3. What are some of the consequences of discrimination against sexual orientation and gender identity minority populations?
4. How can the physician help families support their children who are lesbian, gay, bisexual, transgender, or queer/questioning (LGBTQ+)?

Introduction

Lesbian, gay, bisexual, transgender, or queer/questioning (LGBTQ+) individuals are members of nearly all communities. All pediatricians will have the privilege of caring for an individual from this population at some point in their career. Youth who are LGBTQ+ are a diverse and resilient population who, when supported, grow into healthy, well-adjusted adults. The stigma associated with being LGBTQ+ can result in a host of adverse health outcomes, however. The American Academy of Pediatrics position statement on caring for LGBTQ+ youth clearly states that there is nothing inherently high risk or abnormal about these youth, but that stigma often causes psychological distress, with a resultant increase in risk behaviors.

Stigma may also be encountered in health care settings. Many LGBTQ+ youth have had negative health care experiences and often do not "come out" to the health professionals they consult. As a result, pediatricians caring for these youth may not be aware of their patients' identity. Children and adolescents of all variations of gender identity and sexual orientation will come under the care of a pediatrician during childhood and adolescence, and it is known that adult outcomes are dependent on the level of nonjudgmental support received.

Language concerning sexual orientation and gender identity is important and constantly changing. In this chapter, the most commonly used acronym, LGBTQ+, is used to refer generally to people with diverse bodies, sexual orientations, and gender identities. Longer or different acronyms are used as well, such as LGBTQIAAP+ (lesbian, gay, bisexual, transgender, queer/questioning, intersex, asexual, ally, and pansexual; see Table 57.1 for definitions), with the goal of being more inclusive and acknowledging that certain groups have not been well represented by some labels or acronyms. The plus symbol at the end of LGBTQ+ is used to indicate that this population includes but is not limited to people who identify as lesbian, gay, bisexual, transgender, and queer/questioning, and that a list of letters can never be fully inclusive.

Table 57.1. Glossary of Terms Concerning Sex, Gender Identity, and Sexual Orientation[a,b]

Term	*Definition*
Affirmed gender	An individual's true gender identity.
Agender	A person who does not identify as having a particular gender.
Ally	An individual who supports and stands up for the rights of LGBTQ+ persons and communities.
Asexual	The sexual orientation of individuals who feel little or no attraction to others. Having an asexual orientation is different from choosing to abstain from sex.
Bisexual	The sexual orientation of individuals who develop both same-sex and opposite-sex romantic, physical, and emotional attractions.
Cisgender	A person who identifies as and expresses a gender that is consistent with the culturally defined norms of the sex they were assigned at birth. Used as an adjective.
FTM; affirmed male; trans male/man; transmasculine	Terms used to describe individuals who were assigned female sex at birth but whose gender identity and/or expression is asserted to be more masculine.
Gay	An individual whose romantic, physical, and emotional attractions (ie, sexual orientation) are to persons of the same sex. Often it refers to men, but it may be used to describe a person of any sex with a same-sex orientation. Used as an adjective.
Gender diverse/gender expansive	Umbrella terms used to describe people with gender behaviors, appearances, or identities that are incongruent with those that are culturally normative for their birth sex. Gender-diverse individuals may refer to themselves by many different terms, such as transgender, nonbinary, genderqueer, gender fluid, gender creative, gender independent, or noncisgender. *Gender diverse* is used to acknowledge and include the vast diversity of gender identities that exists. It replaces the formerly used term, "gender nonconforming," which has a negative and exclusionary connotation. Children who do not yet have language to describe themselves as transgender may be referred to by others by one of these terms.
Gender dysphoria	A clinical symptom characterized by a sense of alienation to some or all of the physical characteristics or social roles of one's assigned gender. Gender dysphoria is also the psychiatric diagnosis in the *DSM-5* that focuses on the distress stemming from the incongruence between one's expressed or experienced (ie, affirmed) gender and the gender assigned at birth. Previous versions of the *DSM* included Gender Identity Disorder, which is no longer appropriate to use but may be found in older research.
Gender expression	The diverse means of communicating one's gender to others, such as through behavior and mannerisms, clothing, hair, voice/speech, and roles/activities. Such expression may be the result of conscious or unconscious decisions and may or may not align with social expectations for gender identity or sex assigned at birth.
Gender identity	The internal sense of one's own gender, which may be female, male, a combination of both, somewhere in between, or neither. Gender identity may or may not align with the social expectations for the sex an individual was assigned at birth and results from a multifaceted interaction of biologic traits, environmental factors, self-understanding, and cultural expectations. Gender identity is distinct from sexual orientation.
Genderqueer/nonbinary	Terms to describe or name the identity of an individual whose gender identity is beyond or outside the gender binary categories of man/male and woman/female.
Homosexual	An outdated term that refers to same-sex sexual orientation. This term is often considered abrasive and offensive. Currently preferred terms may include gay, lesbian, or queer, depending on the individual.
Intersex/differences of sex development	An umbrella term used to describe the variety of conditions in which an individual's physical sex characteristics (ie, external genitalia, internal anatomy, chromosomes, or hormone levels) are considered atypical based on categories of male and female. These conditions may be apparent at birth or may be diagnosed later. For some affected individuals, intersex may also be an identity.
Lesbian	A woman whose romantic, physical, and emotional attraction (ie, sexual orientation) is to other women. May be used as an adjective or a noun.
LGBTQ+	Lesbian, gay, bisexual, transgender, or queer/questioning.
MTF; affirmed female; trans female/woman; transfeminine	Terms used to describe individuals who were assigned male sex at birth but whose gender identity and/or expression is asserted to be more feminine.

Table 57.1. Glossary of Terms Concerning Sex, Gender Identity, and Sexual Orientation[a,b] (*continued*)

Term	*Definition*
Pansexual	An individual whose romantic, physical, and emotional attraction (ie, sexual orientation) may be to individuals of any sex or gender identity. Sometimes shortened to "pan."
Queer	Umbrella term used by some individuals to describe having a sexual orientation or gender identity that is beyond or outside societal norms and expectations. Although "queer" was historically a pejorative term for LGBTQ+ people, some LGBTQ+ individuals have reclaimed this term to describe their identities; however, it is not embraced by all members of the LGBTQ+ community.
Sex	An assignment that is made at birth, usually male or female, typically based on external genital anatomy but sometimes on the basis of internal gonads, chromosomes, or hormone levels.
Sexual orientation	A term used to describe an individual's inherent emotional, romantic, or sexual feelings toward other persons in relation to the sex or sexes to which they are attracted. Examples of sexual orientations include but are not limited to gay, lesbian, bisexual, pansexual, asexual, heterosexual/straight, and queer.
Transgender	An adjective used for an individual who identifies and expresses a gender that differs from the sex assigned at birth or, more generally, who experiences or expresses gender differently from what people expect. Gender identity is different from sexual orientation. Transgender individuals can be any sexual orientation, including but not limited to gay, straight, lesbian, or bisexual. The term "transgender" also encompasses many other labels individuals may use to refer to themselves.

Abbreviations: *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; FTM, female to male; MTF, male to female.

[a] This list is not comprehensive. It is important to recognize that language used to describe identities changes over time. PFLAG maintains a "National Glossary of Terms" at https://www.pflag.org/glossary.

[b] Some definitions adapted from PFLAG. National glossary of terms. PFLAG.org website. https://www.pflag.org/glossary. Accessed July 23, 2019 as well as from Rafferty J; American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics*. 2018;142(4):e20182162.

With proper knowledge, skills, and understanding, every pediatrician can be equipped to help all LGBTQ+ youth grow and thrive (Box 57.1).

Incidence

It is challenging to get an accurate estimate of the number of LGBTQ+ youth in the United States. Large-scale surveys indicate that approximately 5% of the adult population identifies as LGBTQ+ or reports being in or having been in a same-sex relationship. Younger adults are more likely to identify as LGBTQ+; thus, it is likely that these percentages will continue to increase over time. The prevalence of sexual minority persons is consistent across all ethnic and socioeconomic groups. Although less research is available specifically about gender identity, studies show that 0.17% to 2.7% of youth identify as transgender or gender diverse in surveys of middle school, high school, and college students in the United States.

Gender Identity and Sexual Orientation

Gender identity, gender expression, and sexual orientation are 3 separate concepts that are often confused and sometimes inaccurately interchanged (see Table 57.1). *Gender identity* refers to an individual's internal sense of self as male, female, some combination of both, an identity in between, or neither, whereas *gender expression* is the way in which individuals present their gender to people around them through outward markers, such as clothing, hair, and mannerisms. It is important to understand and distinguish between gender identity and gender expression. Although gender expression can vary based on cultural expectations and may be influenced by parental and peer support or rejection, gender identity is intrinsic to the self and cannot be changed by external influences.

For most people, gender identity coincides with cultural norms associated with their biologic or natal sex; the word used to describe this alignment is *cisgender*. For some individuals, gender identity is incongruent with cultural norms associated with their biologic sex; the word used to describe this alignment is *transgender*. Gender identity often develops before puberty, as young as 2 to 3 years of age. Many children display variations in gender expression and are gender expansive or gender variant throughout early childhood and into adolescence. Some of these children eventually identify as transgender and some as cisgender. Additionally, some may identify as *nonbinary*, *genderqueer*, *gender-creative*, or *agender*, meaning that their gender identity is something outside the binary of male or female.

In contrast, *sexual orientation* refers to an individual's attraction to others and usually develops in late childhood and adolescence. Traditionally, individuals who experience same-sex attraction have been called *gay* or *lesbian*, those who experience opposite-sex

Box 57.1. Best Practices for Creating an LGBTQ+-Friendly Office

Before the Visit

- Decorate the office with affirming rainbow stickers and posters.
- Brochures, books, and website images should represent the full spectrum of gender expressions and family structures.
- Intake forms should include space for different family structures and gender identities. The forms should include questions about preferred name and gender marker. Examples of such questions can be found here: www.ama-assn.org/delivering-care/creating-lgbtq-friendly-practice.
- Electronic medical records should represent the patient's preferred name and pronoun.
- All office staff should be trained to use open-ended language when discussing family structure and preferred name and/or pronoun.
- Bathrooms should be gender neutral or single stall, and signage should indicate this.

During the Visit

- Provide the same level of care that you would for any patient. Use the American Academy of Pediatrics or the Society for Adolescent Health and Medicine guidelines.
- Use the appropriate pronoun and/or name.
- Discuss confidentiality. Concerns about possible disclosure often are mentioned by LGBTQ+ youth as a reason to avoid seeking health care.
- Use open-ended language during the interview. See Box 57.2 for examples of language to use to ask about sexual orientation and gender identity.
- When asking questions about identity or behavior, explain to the youth the medical reasoning behind the question. Avoid asking invasive questions only to satisfy curiosity. The physician should avoid asking the youth to be the physician's educator about issues of sexuality and gender.
- As for all youth, it is important to know about recommendations for screening based on sexual risk behaviors and to avoid making assumptions about risk based on sexual orientation or gender identity.
- Genital examinations can be particularly traumatic for gender diverse patients. Explain the medical rationale behind the examination and allow the youth as much control over the process as possible.
- LGBTQ+ status is only 1 of the patient's many identities and may not be the main reason for the patient's visit. It is important to conduct routine health maintenance and devote attention to other identities important to the individual patient, such as race, religion, and chronic illness.

After the Visit

- The physician must be the patient's advocate and help families and communities support the child. The physician can provide parents with the information offered in Box 57.3.
- If referrals are necessary, the primary care physician should call ahead to ensure that the specialist or therapist is aware and supportive of the needs of LGBTQ+ youth and families.
- The physician should advocate for LGBTQ+ youth within the school district to encourage implementation of support systems, such as peer organizations and anti-bullying policies.

Abbreviation: LGBTQ+, lesbian, gay, bisexual, transgender, or queer/questioning.

attraction have been called *heterosexual* or *straight*, and those who experience attraction to both sexes have been called *bisexual*. Like all people, those who are transgender can be attracted to a person of any sex or gender, and they may identify as straight, bisexual, gay or lesbian, or something else. It is also important to note that language around sexual attraction shifts with every new generation, and currently it is common to hear youth use new terms and language to more fully describe the complexities of their sex and gender as well as to whom they are attracted.

Intersex Conditions

Intersex conditions are important to consider in discussions of sexual orientation and gender identity, but these states and identities should not be conflated. Individuals with intersex conditions, or differences of sexual development, have bodies that differ from typical male or typical female medically defined sex designations. External genitalia, internal anatomy, chromosomes, or hormone levels are atypical based on categories of male and female. These conditions may be apparent at birth or may be diagnosed later. Historically, and sometimes even currently, those in the medical profession have tried to "correct" these bodies to align individuals' genital appearance with typical male or female definitions. These procedures have at times resulted in harm, such as removal of tissue important for sexual sensation, fertility, and hormone production, or performing a surgical sex assignment that does not align with that person's identity as the individual ages. Many members of the intersex community feel that such irreversible elective procedures performed on young children are harmful and unnecessary and put children and adults at risk; instead, individuals with this view would prefer that these intersex children be left intact and celebrated as existing on the continuum of normal of healthy bodies. Additionally, individuals with certain intersex conditions have increased rates of identity as a member of a sexual or gender minority population compared with the general population. Although the medical needs of intersex individuals are different from those of sexual and gender minority groups, advocacy for people with intersex conditions shares common themes, values, and goals with broader advocacy for the LGBTQ+ community.

Health Consequences of Discrimination

Despite an increase in public dialogue and recent changes in some discriminatory laws, LGBTQ+ youth continue to experience stigmatization and its consequences. Often, LGBTQ+ youth are the objects of bullying, isolation, and family rejection. Individuals at particular risk are those whose gender expression or identity differs from societal expectations; this is especially true for transgender women (ie, assigned male sex at birth but with self-identified female or feminine gender identity) and people of color. National surveys of LGBTQ+ youth show that verbal, electronic, and physical harassment in schools are commonplace and are associated with school avoidance and other far-reaching consequences. Additionally, persons of sexual and gender minority groups are targeted in approximately 20% of violent hate

crimes in the United States. The result of these high rates of victimization is that the lives of many LGBTQ+ youth have been touched by violence or the threat of violence. This trauma is compounded for LGBTQ+ youth who are part of other vulnerable groups, such as people with disabilities, people of color, and immigrants.

Most LGBTQ+ youth are resilient and develop into healthy adults; however, compared with their cisgender heterosexual peers, as a group they are at increased risk for adverse health outcomes, such as suicide attempts, substance use, and risky sexual behavior. It is important for health professionals to understand the key mediators of these adverse health outcomes. Youth who have been victimized or who perceive discrimination are more vulnerable to engaging in high-risk behaviors.

Family support is particularly important for persons who are LGBTQ+. One study showed that LGBTQ+ young adults who experienced higher levels of family rejection during adolescence were 8 times more likely to report suicide attempts, 6 times more likely to report significant depression, and 3 times more likely to use illegal drugs or engage in unprotected sexual intercourse compared with those who did not experience family rejection. Conversely, families that are highly supportive are more likely to have children who are resilient and well adjusted. Family acceptance during adolescence is associated with better general health, self-esteem, and social support in LGBTQ+ young adults.

Youth who are LGBTQ+ are also significantly overrepresented among homeless youth. Studies estimate that up to 40% of homeless youth identify as a person of a sexual or gender minority population. Youth often become homeless resulting from family conflict about their sexual orientation or gender expression. Sexual and gender minority youth are more likely to suffer negative outcomes associated with living on the streets. Physical assault, sexual victimization, substance abuse, and high-risk sexual behavior are all more common for LGBTQ+ homeless youth than for heterosexual cisgender homeless youth.

Transition and Transgender Youth

Transgender youth may choose to undergo a transition in which their gender expression shifts from 1 gender to another. Transition may be different for every individual and can take months or years. It may involve *social transition*, which involves changing one's name, pronoun, and gender expression to align with the gender identity; *medical transition*, which can involve hormones or surgeries to physically change the body; and *legal transition*, which involves changing name and sex marker on documents, such as birth certificates and passports. Decisions around transition are often informed by personal choice, finances, and medical barriers. It is important to note that there is no such thing as a "complete transition," and neither surgery nor medical intervention is necessary to legitimize a person's identity as transgender or fully male or female.

"Reparative" or Conversion Therapy

Care for LGBTQ+ youth involves affirmation and support for their identities. Historically, some religiously and politically motivated groups have used outdated and discredited medical theories to justify trying to "cure" the natural sexual orientation or gender identity of those who are LGBTQ+. Because of the harm caused by this ineffective approach, reparative/conversion therapy is now banned in an increasing number of states and municipalities and is opposed by most professional organizations, including the American Academy of Pediatrics. Although such "therapies" are still practiced within some communities, pediatricians should actively discourage families from pursuing them.

Children With LGBTQ+ Parents

As many as 6 million American children and adults have a lesbian, gay, bisexual, or transgender parent, and combined data suggest that almost 2 million children younger than 18 years in the United States are being raised by at least 1 gay or lesbian parent. Children join families with same-sex parents in a variety of ways, including adoption, assisted reproductive technologies, or from previous heterosexual contact as stepfamilies or blended families. Like all families, families led by LGBTQ+ parents are diverse. These families are more likely to be composed of racial minorities, include adopted children, include children with disabilities, and have lower household incomes than families of opposite-sex couples. Multiple longitudinal and cross-sectional studies indicate that children with same-sex parents do well in domains of social, academic, and total competence. Many studies have shown that children in families headed by same-sex parents in 2-parent households have outcomes similar to children with heterosexual parents.

Important Role of Pediatricians

Pediatric health professionals have a unique opportunity to model acceptance of each patient, provide appropriate risk-reduction counseling, and encourage family support. LGBTQ+ adolescents want the same attributes in their health professionals that other groups of teenagers value, including confidentiality, honesty, respect, competence, and a nonjudgmental approach to history taking and guidance. To maintain a supportive role, the physician must take care to avoid making assumptions. The physician should not assume genital anatomy, the gender of partners, or family constellation. Neutral language should be used until the physician has completed important components of the history (Box 57.2).

It is also critical never to assume information about a person's sexual practices based on that individual's stated gender identity or sexual orientation, because people's identities do not always align with their behavior. In 1 survey, more than twice as many youth reported same-sex sexual experiences as those who eventually identified as gay. These data reinforce the important distinction between sexual orientation and sexual behavior. A wide range of sexual behavior exists in teenagers, and sexual identity formation is a dynamic developmental process. Teenagers who eventually identify as gay may have had heterosexual sexual contact, and those who identify as straight may have had a same-sex experience. For this reason, the pediatrician should be prepared to ask questions about sexual behaviors as well as identity when evaluating the LGBTQ+ pediatric patient.

Equally important is to ask for and use the individual's preferred name and pronoun. Pronouns can be "he," "she," the singular "they," or other nonbinary pronouns. It is most appropriate to refer to people by their gender identity and not by their assigned sex. For example, someone assigned male at birth who identifies as female is called a transgender woman or simply a woman, and she/her pronouns are used. The term transgender is used as an adjective. It is not a noun, as in "transgenders," nor a verb, as in "transgendered." If pronouns or preferred name are not clear, it is acceptable to ask the individual. Health professionals can also show support by avoiding unnecessarily invasive questions about genital status.

Many physicians report that they feel unprepared to care for LGBTQ+ individuals. Part of this process involves learning how to ask and how to respond when a youth answers in the affirmative.

Box 57.2. What to Ask

Gender

- What is your gender? What pronouns do you use?
- Do you consider yourself male, female, both, or neither?
- Some people feel as though there is a mismatch between their sex assigned at birth and the gender they feel themselves to be. Does that resonate with you?

Sexuality

- To whom are you attracted?
- Do you have a partner or partners?
- What is the sex of your partner(s)?
- Are you intimate with your partner?
- What parts of your body do you use for intimacy?

Box 57.3. Supportive Behaviors That Help Families Promote the Well-Being of Their Lesbian, Gay, Bisexual, or Transgender Child

- Talk with your child about his, her, or their lesbian, gay, bisexual, transgender, or queer/questioning (LGBTQ+) identity.
- Express affection when your child tells you or when you learn that your child is LGBTQ+.
- Support your child's LGBTQ+ identity even though you may feel uncomfortable.
- Advocate for your child anywhere he, she, or they is mistreated because of an LGBTQ+ identity.
- Insist that all family members respect your LGBTQ+ child.
- Bring your child to LGBTQ+ organizations or events.
- Connect your child with an LGBTQ+ adult role model to show your child positive options for the future.
- If you are part of a faith community, work to make it supportive of LGBTQ+ members or find a supportive faith community that welcomes your family and LGBTQ+ child.
- Welcome your child's LGBTQ+ friends and partner to your home as well as family events and activities.
- Support your child's gender expression.
- Believe your child can have a happy future as an LGBTQ+ adult.

Adapted with permission from Ryan C. *Supportive Families, Healthy Children: Helping Families with Lesbian, Gay, Bisexual & Transgender Children*. San Francisco, CA: Marian Wright Edelman Institute, San Francisco State University; 2009.

CASE RESOLUTION

The child is displaying behaviors that do not meet his mothers's expectations for male gender expression. The pediatrician should let the mother know that gender expression, sexual orientation, and gender identity are separate and distinct and that a broad range of normal exists for each of these. Neither sexual orientation nor gender identity can be predicted from the behaviors described.

Many adolescents go through a period of questioning their sexuality. The child's mother should be informed that no matter her child's sexual orientation or gender identity, a major risk factor for engaging in unsafe behaviors in adolescence is parental rejection. Attempts to change a person's sexual orientation do not work and are in fact dangerous; they are associated with significant depression and thoughts of suicide. For this child to develop normally, he needs supportive adults in his life—ideally, his parents—who accept and love him.

Particularly because of this child's social withdrawal, it is important to determine if he has been a victim of bullying at school or on sports teams, or if he is experiencing depression. An appointment for the child should be scheduled, and some time should be spent during the visit without his parents present. This will provide an opportunity to evaluate the child's strengths and note if he is displaying any signs of anxiety or depression. The sample questions about gender identity and sexual orientation found in Box 57.2 should be adapted to the developmental stage of the child. The child should be assured that his responses to these questions will be kept confidential. The pediatrician could also facilitate a discussion between the patient and his parents while modeling support and acceptance. An ongoing dialogue with the mother will also help the pediatrician determine if or when referrals to support and educational groups, such as PFLAG (formerly parents, families and friends of lesbians and gays), are appropriate.

Online Resources

Health professionals recognize that patients often come to them having already searched online for the answers to their questions. What follows is a list of reliable organizations to recommend or refer to for more information and support.

For LGBTQ+ Youth

GLSEN (formerly the Gay, Lesbian & Straight Education Network)
www.glsen.org
GLSEN strives to ensure that each member of every school community is valued and respected regardless of sexual orientation or gender identity or expression.

It Gets Better Project
www.itgetsbetter.org
The website offers hundreds of videos of encouragement, and young people who are LGBTQ+ can see the ways in which love and happiness can be a reality in their future. Straight allies can visit the website and support their friends and family members.

National Runaway Safeline
www.1800runaway.org
1-800-RUNAWAY is a confidential and anonymous crisis hotline for runaway and homeless youth available 24 hours a day, 365 days a year.

The Trevor Project
www.thetrevorproject.org
The Trevor Project is a national organization focused on crisis and suicide prevention efforts among LGBTQ+ youth. Trained counselors are ready 24/7 at 1-866-488-7386.

For LGBTQ+ Parents and Their Children

COLAGE: People with a Lesbian, Gay, Bisexual, Transgender or Queer Parent
www.colage.org
COLAGE is a national movement of children, youth, and adults with 1 or more LGBTQ+ parents. COLAGE connects people with LGBTQ+ parents into a peer support network and offers organized events for families as well as youth leadership development opportunities.

Fenway Institute. *Pathways to Parenthood for LGBT People*
www.lgbthealtheducation.org/wp-content/uploads/Pathways-to-Parenthood-for-LGBT-People.pdf
This publication is a readily available resource for information and guidance for potential or current parents as well as health professionals about the various pathways to parenthood for LGBTQ+ people and some of the unique issues faced by LGBTQ+ parents.

For Parents and Others

Family Acceptance Project
familyproject.sfsu.edu
A research-based, culturally grounded approach to help ethnically, socially, and religiously diverse families decrease rejection and increase support for their LGBTQ+ children. The website offers printable handouts in multiple languages.

Gender Spectrum
www.genderspectrum.org
Gender Spectrum provides education, training, and support to help create a gender-sensitive and inclusive environment for all children and teenagers. It provides resources to help families, educators, professionals, and organizations understand and address the concepts of gender identity and expression.

PFLAG (formerly Parents, Families and Friends of Lesbians and Gays)
https://pflag.org
PFLAG promotes the health and well-being of LGBTQ+ persons, their families, and friends through support, education, and advocacy.

For Professionals

American Academy of Pediatrics Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness
www.aap.org/en-us/about-the-aap/Sections/Section-on-LGBT-Health-and-Wellness/Pages/SOLGBTHW.aspx
The mission of this American Academy of Pediatrics section is to support the health and wellness of LGBT children and their parents/guardians, families, and health providers; children with variations in gender presentation; as well as LGBTQ+ pediatricians and trainees.

Centers for Disease Control and Prevention Lesbian, Gay, Bisexual and Transgender Health Website
www.cdc.gov/lgbthealth/index.htm
The perspectives and needs of LGBT people should be routinely considered in public health efforts to improve the overall health of every person and eliminate health disparities.

Fenway Institute
https://fenwayhealth.org/the-fenway-institute
The Fenway Institute is dedicated to advancing the skills, attitudes, and knowledge of clinicians and other health professionals by providing professional development, educational materials, and resources on LGBTQ+ health topics. The website offers several online educational modules for physicians.

GLMA: Health Professionals Advancing LGBTQ Equality (formerly Gay and Lesbian Medical Association)
www.glma.org
The mission of GLMA is to ensure equality in health care for LGBTQ+ individuals and health professionals. The GLMA website features an online provider directory and educational materials.

Society for Adolescent Health and Medicine
www.adolescenthealth.org/Resources/Clinical-Care-Resources/Sexual-Reproductive-Health.aspx
This website offers a variety of information of sexual and reproductive health information for adolescents categorized by target population, including providers, parents, and teenagers.

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CHAPTER 58

Reproductive Health

Monica Sifuentes, MD

CASE STUDY

An 18-year-old female college student in good health comes in for a routine health maintenance visit during her spring break. She is unaccompanied by her parents and has no complaints, stating that she just needs a checkup. She enjoys college, passed all her fall and winter classes, and has some new friends. She denies tobacco use but says many of her friends smoke e-cigarettes. She occasionally drinks alcohol and has tried marijuana once. Although she is not currently sexually active, she is interested in discussing contraceptive options. Her last menstrual period, which occurred 2 weeks previously, was normal. She is taking no medications. Her physical examination is entirely normal.

Questions

1. What issues are important to discuss with adolescents at reproductive health maintenance visits?
2. What are the indications for a complete pelvic examination?
3. When is a Papanicolaou test indicated as a part of the reproductive health visit?
4. What methods of contraception are most successful in adolescent patients? What factors about each method should be considered?
5. What are the legal issues involved in prescribing contraception to minors in the absence of parental consent?

Adolescent visits to primary care physicians are relatively infrequent by the time teenagers reach puberty. At most, the healthy adolescent patient is seen once or twice during high school for preparticipation sports or camp physicals. If an adolescent is not involved in athletics or if activities in which the adolescent is involved do not require periodic assessments, such a teenager will rarely visit a health professional while in high school except for an acute illness. Therefore, it is extremely important to use any interaction with an adolescent as a unique opportunity to provide anticipatory guidance and health education, particularly reproductive health education. This chapter is largely devoted to a discussion of the reproductive health of adolescent females. However, the Evaluation section is divided into 2 sections, 1 for females and 1 for males. The reader is referred to Chapter 60 for more information on sexually transmitted infections.

Reproductive health is multidimensional and includes sexuality-related services, screening for communicable infections, anticipatory guidance, and counseling. Such services should be included as a part of the routine health maintenance examination for male and female adolescents for several reasons. The high incidence of sexually transmitted infections (STIs) in this age group, the risk of acquiring HIV, and the reality of an unplanned pregnancy make reproductive health issues increasingly important for teenagers and young adults. Additionally, adolescents rarely schedule appointments with primary care physicians prior to the initiation of coitus. Experimentation with drugs and alcohol at this time in their lives also contributes to early, unplanned sexual experiences (Box 58.1).

Aside from issues of sexual activity, the adolescent also may have questions about the progression through puberty. Normal variants in body habitus or certain physical characteristics can be a source of unnecessary anxiety for the uninformed teenager. Health education to alleviate these fears is ideal. The adolescent who is seen for a health maintenance examination should be allotted extra time so that topics such as puberty, abstinence, gender identity, sexual behaviors and activity, STIs, and contraception can be discussed. Additionally, during more acute, problem-oriented visits, the adolescent should be encouraged to voice any other concerns he or she may have. Depending on the nature of these issues, follow-up appointments can be scheduled.

Normal Secondary Sexual Development

Puberty begins during early adolescence with the development of secondary sexual characteristics. Because of the tremendous variation in the age, duration between pubertal stages, and somatic growth of adolescents, a sexual maturity rating (SMR [ie, Tanner stage]) is used to describe breast and pubic hair development in females and genital development and pubic hair growth in males (Figures 58.1, 58.2, and 58.3). The average age of menarche in the United States is 12.5 years, which for most females occurs during SMR 3 and 4. In contrast, spermarche occurs early in pubertal development in boys, at approximately 13 years of age, with little to no pubic hair development. Full fertility is generally achieved by age 15 years, or mid-adolescence, in most boys and girls.

Box 58.1. Reproductive Health: Sexual Activity

Statistics on sexual activity among adolescents in the United States have changed over the last decade. Previously, it was reported that 1 in 4 females and 1 in 3 males had had sexual intercourse by 15 years of age. Currently, only 13% of teenagers have ever had vaginal intercourse by age 15, according to the Guttmacher Institute. Currently, most adolescents are waiting to initiate sexual activity; by their 19th birthday, 7 in 10 teenagers of either sex have had sexual intercourse. Contraceptive use at first premarital sexual encounter has increased to nearly 80% in adolescent females and 87% in adolescent males; however, unintended pregnancy and sexually transmitted infections (STIs) continue to be a major public health concern for this age group. Although the pregnancy rate among teenagers has dropped steadily over the past 10 years, each year nearly 850,000 adolescent females younger than 20 years become pregnant. Most of these pregnancies are unintended and occur premaritally, especially among certain racial and ethnic minority groups. The outcome of these pregnancies in 15- to 19-year-olds varies. An estimated 50% to 60% of these pregnancies result in live births, 30% end in abortion, and 10% to 15% are miscarried or stillborn.

Unprotected sexual activity among adolescents has several adverse health consequences, the most obvious being teenage pregnancy. Of the adolescents who continue their pregnancies, preterm birth (<37 weeks' gestational age) and low birth weight (<2,500 g [5.5 lb]) are 2 of the most frequently reported neonatal complications. Long-term maternal psychosocial sequelae of adolescent pregnancy include undereducation/school failure, limited vocational training and skills, economic dependency on public assistance, subsequent births, social isolation, depression, and high rates of separation and divorce among teenage couples.

In addition to unintended pregnancy, the risk of contracting an STI, such as chlamydia, human papillomavirus, herpes, and HIV, is increased. In cases of pelvic inflammatory disease from gonorrhea or chlamydia, future problems with fertility and an increased risk of ectopic pregnancy can occur. Human papillomavirus, which is associated with the development of genital warts, cervical dysplasia, and cancer, accounts for approximately one-half of STIs diagnosed in adolescents and young adults. The prevalence rates of other STIs, such as chlamydia and gonorrhea, are still highest among 15- to 19-year-old females compared with older age groups in the United States. More alarming, however, is the relationship between AIDS in young adults aged 20 to 29 years and probable exposure to HIV during adolescence.

Many factors have been associated with the initiation of early coitus in adolescents. They include male sex; race/ethnicity; poverty; a large, single-parent family; previous teenage pregnancy in the household, whether of the mother or a sibling; poor academic achievement; discrepancy between the onset of physical puberty and cognitive development; peer group encouragement; and problem behaviors, such as drug use. Additionally, religious affiliation and cultural norms likely influence this decision. The role of hormonal changes during puberty and their influence on behavior remains unknown.

The adolescent with an intellectual disability that may or may not be associated with chronic illness requires special consideration in terms of reproductive health. With recent advances in medical therapy for conditions such as diabetes mellitus and sickle cell disease, many of these adolescents experience normal pubertal development and fertility. Like their healthy peers, some begin engaging in sexual intercourse at an early age. Unintended pregnancy and childbirth can exacerbate some chronic illnesses and can increase health risks significantly for both the adolescent and developing fetus. The genetic implications and specific patterns of inheritance of certain medical conditions must also be considered. Thus, attention to sexual issues is essential for the adolescent or young adult with chronic medical illness and/or intellectual disability.

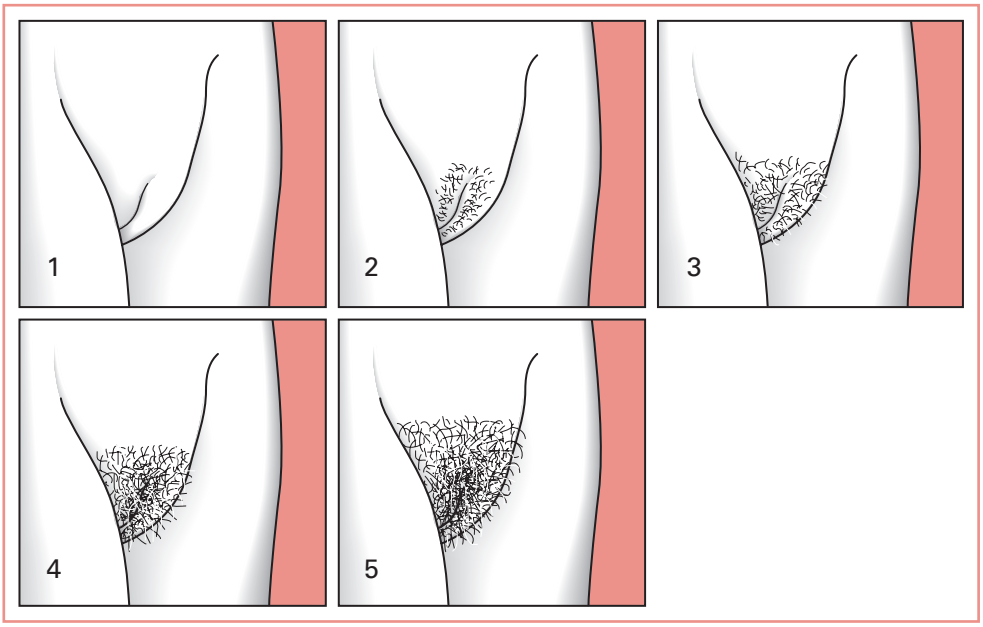

Figure 58.1. Female pubic hair development. Sexual maturity rating 1: prepubertal, no pubic hair. Sexual maturity rating 2: straight hair is extending along the labia and between ratings 2 and 3, begins on the symphysis pubis. Sexual maturity rating 3: pubic hair is increased in quantity; is darker, coarser, and curlier; and is present in the typical female triangle. Sexual maturity rating 4: pubic hair is more dense, curled, and adult in distribution but is less abundant. Sexual maturity rating 5: abundant, adult-type pattern; hair may extend on the medial aspect of the thighs.

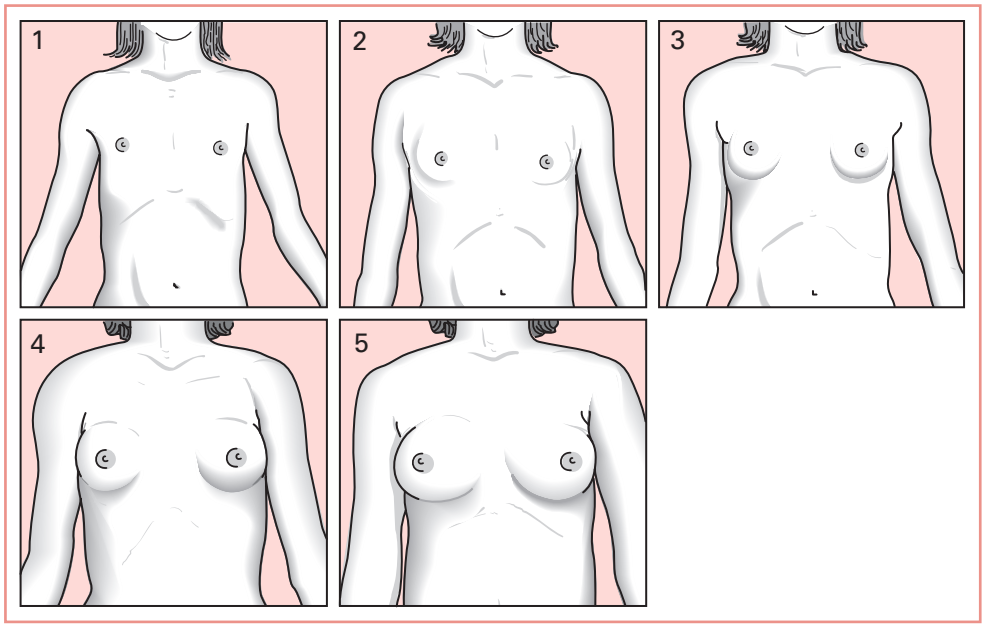

Figure 58.2. Female breast development. Sexual maturity rating 1: prepubertal, elevations of papilla only. Sexual maturity rating 2: breast buds appear, areola is slightly widened and projects as small mound. Sexual maturity rating 3: enlargement of the entire breast with no protrusion of the papilla or of the nipple. Sexual maturity rating 4: enlargement of the breast and projection of areola and papilla as a secondary mound. Sexual maturity rating 5: adult configuration of the breast with protrusion of the nipple, areola no longer projects separately from remainder of breast.

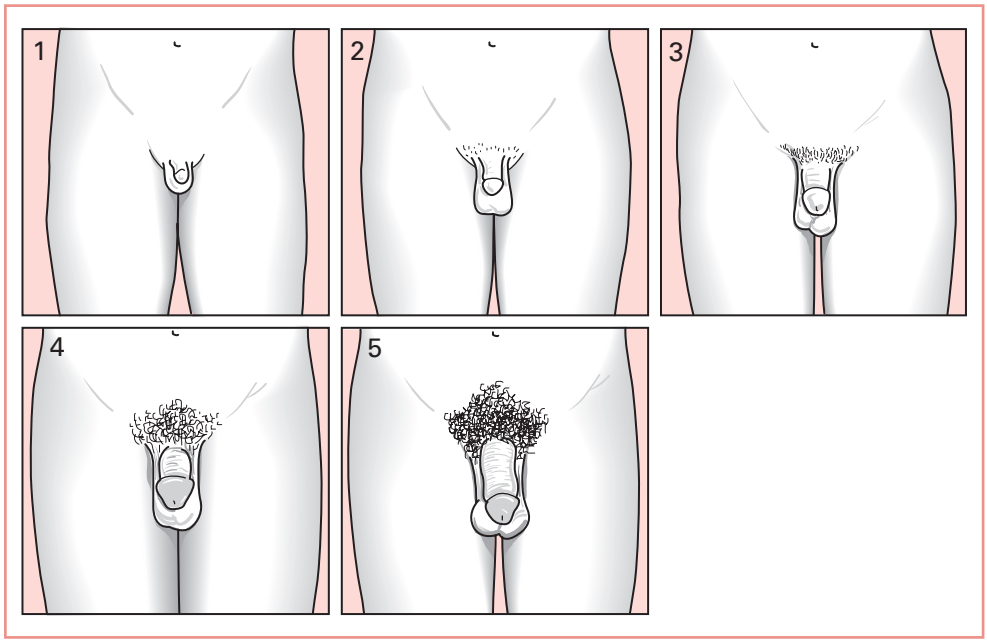

Figure 58.3. Male genital and pubic hair development. Sexual maturity rating 1: prepubertal, no pubic hair, genitalia unchanged from early childhood. Sexual maturity rating 2: light, downy hair develops laterally and later becomes dark; penis and testes may be slightly larger; scrotum becomes more textured. Sexual maturity rating 3: pubic hair is extended across pubis; testes and scrotum are further enlarged; penis is larger, especially in length. Sexual maturity rating 4: more abundant pubic hair with curling, genitalia resemble those of an adult, glans has become darker. Sexual maturity rating 5: adult quantity and pattern of pubic hair, with hair present along the inner borders of the thighs. The testes and scrotum are adult in size.

Evaluation

History

The history obtained at a reproductive health visit should include 2 parts: the medical history, which in females focuses primarily on the gynecologic history, and the psychosocial interview. Regardless of the type of visit scheduled, the physician should take a few moments at the beginning of the interview to address routine health maintenance issues with the adolescent (Box 58.2). For the female patient, the primary care physician should ask whether she has ever undergone a genital or pelvic examination. Additionally, current methods of contraceptive use, if any, should be reviewed (Box 58.3). If the adolescent female has just started taking oral contraceptives, compliance, common side effects, and a review of the more emergent complications of birth control pills is warranted, especially at an initial visit. The acronym ACHES (abdominal pain, chest pain, headaches, eye problems, severe leg pain) is useful to remember life-threatening reactions that can be associated with hormonal contraceptive use (Box 58.4), although these reactions are uncommon in otherwise healthy adolescent girls. If the adolescent is using another form of contraception, adherence to and satisfaction with the particular method should be reviewed along with the respective common side effects. The physician should specifically inquire if the adolescent desires to continue the same method of birth control or is interested in another method.

The remainder of the psychosocial history, otherwise known as the HEADSS assessment (home, employment and education, activities, drugs, sexuality, suicide/depression), should be completed regardless whether the adolescent is currently sexually active (see Chapter 4). Risk factors for an unplanned pregnancy or unintentional exposures to STIs should be kept in mind when formulating a health care plan with the teenager.

Box 58.2. What to Ask

Reproductive Health

For Males and Females

- How is the adolescent feeling overall?
- Has the adolescent had any recent illnesses or conditions that the health professional should know about?
- When was the last physical examination performed? Did it include a genital or pelvic examination?
- Is the adolescent sexually active?
  - If so, are their sexual relationships with males, females, or both?
  - When was the last episode of vaginal or anal intercourse?
  - Was the last episode of sexual intercourse protected or unprotected?
  - Does the adolescent have oral sex?
  - How old was the adolescent when he or she they began having sexual relationships? Was it consensual? Coerced? Forced?
  - How many sexual partners does the patient have currently? How many sexual partners has the patient had in his or her lifetime?
- Is there any history of or ongoing physical or sexual abuse?
- Has the adolescent or any of the adolescent's partners ever been treated for a sexually transmitted infection or tested for HIV?

For Females Only

- What was the age at menarche?
- What was the date of the last menstrual period and the duration and amount of flow?
  - Are any symptoms, such as cramping, bloating, or vomiting, associated with menses?
  - Are any of these symptoms incapacitating? Do they cause the adolescent to miss school or work?
  - Does the mother or do any siblings have similar problems? If so, how do they manage them, if at all?

Box 58.3. What to Ask

Contraceptive Use

- Does the adolescent use condoms never, sometimes, or always?
- Is any other method of birth control also used?
- Is the adolescent female currently using oral contraceptives?
  - If so, what particular type is she taking, and how long has she been using this method of contraception?
  - How often does she miss taking the pill? What does she do when she fails to take the pill?
  - Does she experience common minor side effects, such as breakthrough bleeding, headache, or nausea?
- Is the adolescent female using a long-acting progestin, such as Depo-Provera? If so, has she experienced irregular bleeding, weight gain, hair loss, headache, or acne?
- Is there another method of contraception that the adolescent has used or might be interested in discussing or starting, such as long-acting reversible contraception?
- What does the adolescent know about emergency contraception?

Box 58.4. Danger Signs Associated With Oral Contraceptive Use

A	Abdominal pain (severe)
C	Chest pain (severe) with shortness of breath
H	Headaches
E	Eye problems (visual loss or blur)
S	Severe leg pain (calf and/or thigh)

Physical Examination

A complete physical examination should be performed on all adolescents, with particular attention paid to SMR, blood pressure, and growth chart. A chaperone should be present during the physical examination, particularly during the breast and genital examination, even if the patient and examiner are the same sex.

Males

The genitalia should be examined closely for penile and testicular size, distribution of pubic hair, and presence of any ulcerative,

vesicular, or wart-like lesions. Any urethral erythema or discharge should be noted. Testicular masses require further evaluation. Ideally, the physician should use this opportunity to teach the male adolescent how to perform a testicular self-examination.

Females

Before performing the physical examination, the physician should determine whether a full-speculum examination is indicated (Box 58.5). This decision should be based on the details of the individual case and not solely on the basis of sexual activity. With the advent of noninvasive screening methods for STIs, a routine pelvic examination often is unnecessary and not required before initiating contraception. Most experts now recommend the use of urine or vaginal-based nucleic acid amplification tests (NAATs) to screen for gonorrhea or chlamydia in lieu of endocervical swabs. If a speculum examination is indicated, however, proper preparation of the adolescent is imperative. This should include an explanation of the procedure and the physical sensations felt while the speculum is being inserted and the endocervical specimen is being obtained. In addition to a chaperone, the choice of who should be present during the examination (eg, parent or friend who may have accompanied the patient) and a discussion of the desired positioning (ie, supine or semi-sitting) are also important points to review with the patient. Additionally, the speculum, specimen swabs, and other equipment should be shown to the adolescent before she is draped. The goal is to minimize the adolescent's fears, anxieties, misconceptions, and discomfort about the examination.

A breast examination should be performed on female adolescents, and any breast tenderness, nodularity, or masses should be noted. This portion of the examination can be used to educate the patient about the purpose and importance of breast self-examinations and to document breast SMR.

The external genitalia should be examined in all adolescent females at least once during puberty regardless whether they are sexually active. The SMR and any congenital anomalies, such as asymmetric enlargement of the labia minora or an imperforate hymen, should be identified. In the sexually active adolescent, the external genitalia should be carefully examined for warts, ulcers, and vesicular lesions. Any urethral erythema, edema, or discharge that may indicate an otherwise asymptomatic chlamydial infection should be noted. If a pelvic examination is indicated, a vaginal discharge may be appreciated before inserting the speculum; ideally, however, the cervix should be examined for cervical ectopy, friability, and any lesions or discharge from the os. The vaginal mucosa should also be inspected as the speculum is withdrawn.

During the bimanual examination, the cervix should be palpated for any cervical motion tenderness. Uterine size and position should be appreciated, and adnexal tenderness or masses should be noted. Because normal ovaries are approximately the size of almonds, many physicians do not palpate them. A rectovaginal examination is necessary to rule out fistulas, especially in the postpartum adolescent. If the physician is unable to perform a vaginal bimanual examination, a rectoabdominal examination can be done to assess uterine size and position and the presence of adnexal masses.

Box 58.5. Indications for a Complete Pelvic Examination

- Pregnancy
- Request by the adolescent
- Unexplained lower abdominal pain
- Persistent abnormal vaginal discharge
- Unexplained vaginal bleeding
- Dysmenorrhea that is unresponsive to nonsteroidal anti-inflammatory drugs
- Suspected or reported sexual assault
- Perform a Papanicolaou test

Laboratory Tests

Because most *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in adolescents are asymptomatic, screening for these organisms via noninvasive urine-based or vaginal NAATs is recommended annually in all sexually active adolescents and more frequently in those who have a history of unprotected intercourse or a new sexual partner. If the adolescent has a vaginal discharge or cervical friability noted on speculum examination, the specimen should be obtained directly from the endocervix. A saline and potassium hydroxide wet mount should also be collected from the symptomatic patient. A Papanicolaou (Pap) smear should be performed in sexually active females who are 21 years or older. Although the Pap smear may detect *Trichomonas vaginalis* or the cytologic changes associated with human papillomavirus infection, routine screening in asymptomatic adolescents is not recommended. A NAAT (eg, polymerase chain reaction) for human herpesvirus should be performed if painful vesicles are noted on examination. As clinically indicated, a fresh vesicle can also be unroofed and a specimen sent for herpesvirus cell culture or NAAT.

Other laboratory tests include a rapid plasma reagin test for syphilis and an HIV screening test in the adolescent identified as high risk or at least annually. Baseline complete blood cell count, liver function tests, cholesterol, and hemoglobin A_{1C} may be indicated as part of the health maintenance visit but are not required before starting contraception. A pregnancy test is warranted in the sexually active female if the physician chooses to begin oral contraceptives or another method of hormonal contraception mid-cycle ("quick start" method) or if menses are late.

Management

Reproductive Health Education

All management plans during reproductive health visits should include a frank discussion of puberty, gender identity, sexual orientation, sexual behavior, and STIs regardless of current or prospective sexual activity. The adolescent also should be counseled about abstinence as an acceptable choice. Ideally, preventive health care measures, such as breast and testicular self-examinations, have been

reviewed during the physical examination. It is hoped that by encouraging adolescents' familiarity with these self-examinations, they will continue to perform them throughout their adult lives. The use of posters, plastic models, and electronic or written materials to reinforce the discussion is strongly encouraged. The goal of reproductive health education is to assist adolescents in identifying and communicating their thoughts and feelings about sexual abstinence as well as sexual activity and to aid in the prevention of unintended pregnancy, young parenthood, and STIs. Prevention programs offered by schools must be supplemented by open parental communication in the home about sexuality, although this varies considerably by family.

Legal Issues

The issue of confidentiality is important to consider when providing reproductive health care for the adolescent. Parental involvement should be strongly encouraged; however, health professionals are not required to disclose any confidential information to parents or guardians except in cases of suicidal ideation, harmful intent to others, and sexual or physical abuse. In most states, contraceptive services can be provided to adolescents age 12 years and older without specific knowledge or consent of a parent or guardian. In the United States, the complex issue of parental consent and pregnancy termination varies from state to state and should be reviewed by the individual health professional based on the state in which that individual practices medicine. All 50 states and the District of Columbia explicitly allow minors to consent for their own health services for STIs and do not require parental consent for STI care. Providing confidential care for adolescents enrolled in private health insurance plans, however, remains a difficult issue because many states mandate that health plans provide a written statement to the beneficiary about the services covered and received, including clinical services provided confidentially to teenagers.

Pap Smear

The recommendation of the American College of Obstetricians and Gynecologists is that cervical cancer screening should begin at 21 years of age. After the initiation of screening, a Pap smear for average-risk women age 21 through 29 years should be performed every 3 years. The rationale for not screening teenagers for cervical cancer is that there is little risk in not treating abnormal cervical cytology in adolescents because in this age group 90% to 95% of low-grade lesions, as well as many high-grade lesions, regress to normal spontaneously. Premature screening can result in an overdiagnosis of cervical dysplasia and an overtreatment of lesions with potentially harmful procedures, such as excision or ablation of the cervix. Because the incidence of cervical cancer is quite low among adolescents, the benefits of the Pap test are offset by the potential harm of unnecessary procedures and treatments in this young age group.

Contraceptive Methods

The appropriate method of contraception should be individualized according to the needs and acceptability for each adolescent. The risks, benefits, and limitations of the various contraceptive modalities should be discussed to maximize effectiveness, minimize discontinuation, and avoid contraceptive failures.

Barrier methods include male and female condoms, which have a typical pregnancy failure rate of 15% when used alone but provide protection against many STIs. Nonlatex male condoms are available for individuals with latex allergies; however, these condoms have an increased risk of slippage and breakage. Vaginal spermicides, such as nonoxynol-9, are available in a variety of forms (ie, foams, gels, films, suppositories) and should be used in conjunction with a barrier method because general concerns exist that these products in high doses can increase the risk of genital ulceration and irritation, thereby facilitating STI acquisition.

Hormonal contraceptive methods include combination oral contraceptives (COCs), the transdermal patch, the intravaginal ring, injectable long-acting progestin agents, and long-acting reversible contraceptives, such as the subdermal implantable rod and intrauterine devices (IUDs). Although previously not recommended but now offered for nulliparous teenagers, the levonorgestrel IUD is a highly effective and cost-efficient reversible contraceptive method that requires little compliance, making it especially useful for adolescents. Previous reports about increased rates of pelvic inflammatory disease in teenagers with IUDs are unsubstantiated. The withdrawal method, or coitus interruptus, and natural family planning are ineffective methods for adolescents for protection against pregnancy.

Hormonal Contraception

Combination oral contraceptives are an effective means of birth control for adolescents, with most pills containing 30 to 35 mcg ("low dose") to 20 mcg ("very low dose") of ethinyl estradiol (ie, a synthetic estrogen) and a progestin. Monophasic pills contain a fixed dose of estrogen and progestin throughout the 21-day pill cycle. Biphasic preparations contain a lower dose of the progestin component during the first 10 days of the cycle but are rarely used in teenagers. In triphasic pills, the doses of estrogen and progestin, or the progestin component alone, are varied 3 times throughout the cycle. This contraceptive was created to decrease the overall progestin-related side effects, such as hypertension, acne, and lipid abnormalities, but has not been shown to have any great advantage over a monophasic pill. Most recently, very low-dose monophasic estrogen (20 mcg) pills have been developed to minimize estrogen-related side effects and decrease discontinuation rates. However, 20-mcg estrogen pills may be associated with a higher rate of intermenstrual bleeding and less bone mass acquisition than 30- to 35-mcg pills, especially in young patients. Because of this, monophasic pills with 30 to 35 mcg of ethinyl estradiol are considered the first-line therapy for most teenagers who wish to use COC. Specific instances may exist, however, in which the lower efficacy of these pills must be taken into account and the ethinyl estradiol dose increased to 50 mcg, such as in patients concurrently receiving medications that increase the metabolism of synthetic steroids (eg, certain anticonvulsant agents).

Another COC regimen is 3-month continuous hormonal therapy followed by 1 week of withdrawal bleeding for young women

who prefer to menstruate only 4 times a year, that is, an extended-cycle pill. To reduce the frequency of breakthrough bleeding often experienced by users of the extended-cycle pill, another product is now available that replaces the placebo pills with 7 days of low-dose estrogen.

Progestin-only pills, referred to as minipills, also are available and are particularly useful in postpartum and lactating teenage mothers and for women with contraindications or an intolerance to estrogen. Because ovulation is not consistently inhibited by progestin-only pills, however, they must be taken at the same time every day, because the effect of cervical mucus thickening diminishes in 22 hours.

Clear medical benefits associated with COC use include prevention of pregnancy, protection against ovarian and endometrial cancers, decreased risk of functional ovarian cysts and benign breast conditions, improvement of acne, and decreased menstrual blood loss and menstrual symptoms, such as dysmenorrhea. The most common side effects of COCs include breakthrough bleeding, nausea, and breast tenderness, which generally resolve after 3 cycles. Although potential risks of COC include venous thromboembolic events, hypertension, and changes in the lipid profile, actual risks are minimal in most healthy adolescents without a personal or family history of thromboembolic events compared with the morbidity and mortality associated with teenage pregnancy and childbirth.

Other combined hormonal contraceptive methods for the adolescent include the vaginal ring (eg, NuvaRing, Annovera) and the transdermal patch (eg, Ortho Evra, Xulane). Approved in 2001, the vaginal contraceptive ring is a soft, flexible device that contains estrogen and progestin, which is released directly through the vaginal wall into the bloodstream. The ring is inserted into the vagina for 3 weeks, then removed for 1 week to allow for a withdrawal bleed. The ring can also be removed intermittently for up to 3 hours and remain effective. Systemic side effects are similar to other low-dose combined hormonal methods (eg, headache, breast tenderness, nausea, breakthrough bleeding and/or spotting); specific local effects include vaginal discharge and discomfort secondary to local irritation. Sensation of a foreign body and expulsion of the ring during coitus may also occur. The teenager must be comfortable with insertion and removal of the device for successful use of this method.

The transdermal adhesive patch is a thin, beige, 3-layered plastic patch that contains estrogen and progestin and is applied weekly to specific areas of the body (ie, lower abdomen, upper torso, upper arm, or buttocks) to complete the application of 1 patch per week for a total of 3 weeks, followed by 1 week patch-free during which menses occurs. Although these patches are well tolerated, high complete or partial detachment rates in teenagers have been documented. Additionally, an adolescent may have concerns about the visibility of the patch. Side effects are similar to those of other combined hormonal methods of contraception. Local effects include skin irritation, redness, and rash at the site of application. Reduced effectiveness has been reported in women weighing more than 198 lb (>90 kg). Additionally, concerns have been cited by the US Food and Drug Administration (FDA) about the risk of venous thromboembolic events associated with the patch, although conflicting data have been reported. The reader is referred to the article by Trenor et al in Selected References for a comprehensive review of this topic.

The long-acting injectable progestin depot medroxyprogesterone acetate (DMPA) (eg, Depo-Provera) is given intramuscularly every 3 months (12–14 weeks) to inhibit ovulation, thicken cervical mucus, and induce an atrophic endometrium; a subcutaneous formulation is also available. The most common side effect is irregular menstrual bleeding, especially in the first few months, and eventual amenorrhea with prolonged use. Weight gain remains a significant issue for some patients, particularly in the adolescent with overweight or obesity in whom exaggerated increases in weight occur. Breast tenderness and mood disturbances occur less frequently than weight gain. In 2004, the FDA issued a black box warning for DMPA about possible irreversible bone loss in women with long-term use of DMPA and a potential reduction in overall bone mineral density in teenagers that may contribute to the development of osteoporosis later in life. The FDA therefore recommends that DMPA should not be used in adolescents for longer than 2 years; however, many experts believe that the risk for pregnancy using an inferior method of birth control far outweighs the risk for the development of osteoporosis in a healthy teenager. Ongoing studies suggest that although an adolescent may not increase her bone mineral density while receiving DMPA and does experience bone loss, the effects appear to be temporary and reversible with the discontinuation of DMPA. The adolescent desiring this method of contraception should be made aware of the black box warning and receive adequate calcium and vitamin D and recommend supplementation if the diet appears suboptimal.

A subdermal implant (eg, Implanon, Nexplanon) is available for young women who desire a long-acting reversible method of contraception and has gained popularity as a good option for most adolescents because it requires no compliance after insertion. It is designed to deliver a low, steady dose of continuous progestin for 3 years via a single plastic polymer rod placed below the skin. Formal instruction for insertion and removal is required for the health professional interested in providing this form of contraception. The subdermal implant is highly effective; however, as with other long-acting progestin-only contraceptives, it is associated with bleeding irregularities, especially during the first year of use, which may contribute to its early discontinuation.

Other long-acting reversible contraceptives include levonorgestrel-releasing intrauterine systems (eg, Mirena, Skyla) and the copper IUD (ParaGard). Although previously not recommended for nulliparous women, including teenagers, Mirena was approved by the FDA in 2009 for treatment of severe menorrhagia and dysmenorrhea and is effective for up to 5 years. The Skyla IUD releases a lower dose of levonorgestrel and is approved for 3 years. An increased risk of pelvic inflammatory disease was previously thought to be associated with IUDs in teenagers, but this belief is no longer supported by

the literature. Side effects of intrauterine systems include headache, acne, and breast tenderness as well as irregular menstrual bleeding, particularly during the first 3 to 6 months of use. Additionally, 50% of women develop amenorrhea after 1 year of intrauterine system use. The copper IUD is approved for 10 years of effective long-term contraception and can be used for emergency contraception (EC) as well.

Emergency Postcoital Contraception

Emergency contraception (ie, the "morning-after pill") is an effective means of preventing unintended pregnancy in adolescents by providing high-dose progestin up to 5 days after unprotected intercourse. It requires, however, that the health professional educate teenagers about its availability and usage and that teenagers feel comfortable contacting their physician, if necessary, within 72 to 120 hours of unprotected or inadequately protected intercourse. Although EC is not meant to be used repeatedly as the sole method of contraception, it is useful for the unplanned sexual encounter, which is often the case with adolescents, or after a failed contraceptive method (eg, condom breakage) or sexual assault. Although different EC regimens exist, the most frequently used EC contains a total dose of 1.5 mg of levonorgestrel in a 1- or 2-dose regimen (eg, Plan B One-Step, Next Choice One Dose, My Way). Emergency contraception acts primarily by delaying or inhibiting ovulation. Levonorgestrel-based EC does not interrupt or disrupt an already established pregnancy and is not an abortifacient. Because levonorgestrel EC is not teratogenic, a pregnancy test is not required before its use.

The original EC regimen is a combination of high-dose estrogen and progestin, known as the Yuzpe method; however, nausea and vomiting occurs in approximately 25% to 30% of patients. To reduce these side effects, 2-pill formulations of progestin-only EC (eg, Plan B, Next Choice) are available, consisting of 2 doses of 0.75 mg of levonorgestrel taken 12 hours apart within 3 days of unprotected intercourse. Based on data reported by the World Health Organization, however, this regimen has been modified to take both pills at once up to 5 days after unprotected or inadequately protected intercourse. As a result, Plan B One-Step and its generic forms are now available as a single-pill regimen of 1.5 mg of levonorgestrel, which may improve adherence.

In the United States, progestin-only EC is now available over-the-counter without age restrictions and can be purchased from a pharmacy without the need to show identification. Some state laws also allow pharmacists to provide EC pills directly to individuals of all ages without requiring a doctor's prescription. Emergency contraception is most effective when used within the first 24 hours after unprotected coitus. Although side effects are less common than with the Yuzpe method, the side effects of single-dose progestin-only EC include nausea, vomiting, breast tenderness, and irregular bleeding patterns (eg, spotting); shortened interval to menses; and lighter or heavier menses. Because EC is safe and highly effective in preventing pregnancy, the physician should provide the sexually active teenager with information about the different types of EC, where and how to obtain it, and a prescription (for insured patients, if necessary) at the annual preventive health care visit.

Another type of EC, ulipristal acetate (eg, Ella), is a progestin receptor agonist/antagonist with a mechanism of action similar to levonorgestrel EC; it primarily works by delaying or inhibiting ovulation. Important differences, however, must be considered between ulipristal acetate and progestin-only EC. First and foremost, ulipristal acetate is more effective than progestin-only pills, particularly on the fifth day after sex. It also is more effective closer to the time of ovulation, when women are at greatest risk of pregnancy. Recent data also suggest that ulipristal acetate may be more effective for women with overweight or obesity (body mass index ≥26 or weight >74.8 kg [>165 lb]). Finally, ulipristal acetate is available only with a prescription, regardless of age. Pregnancy must be excluded before prescribing ulipristal because of the risk of fetal loss if used inadvertently in the first trimester of pregnancy. Patients also must be counseled to seek immediate medical attention if they become pregnant or experience severe lower abdominal pain within 6 weeks after its use, because ectopic pregnancy can occur. Common side effects of ulipristal acetate include headache, nausea, and abdominal pain.

Regardless of the type of EC used, the patient should be scheduled for a follow-up office or clinic appointment 2 to 3 weeks after using EC so that a repeat pregnancy test can be performed, treatment failures can be identified early, STI screening can occur, and consistent contraceptive options can be discussed.

Nonhormonal Contraception

Numerous studies and clinical experience have shown that nonhormonal methods are less effective in adolescents than in adults. Latex condoms in conjunction with a spermicide have become a crucial method of contraception since the emergence of AIDS, however. Although they help prevent transmission of some STIs, such as gonorrhea, chlamydia, trichomoniasis, and HIV, condoms do not protect against human papillomavirus and human herpesvirus infection overall because the genital area is not completely covered. Thus, the physician should take time during the office visit to explain these details and demonstrate proper use of condoms. Risks of condom use are minimal, except for allergic reactions to the spermicide, latex, or lubricants. The female condom is not widely used by adolescents but may be helpful in situations in which a male partner refuses to wear a condom. The inner ring may be inserted into the vagina up to 8 hours before intercourse, and neither a prescription nor physician visit is necessary to obtain a female condom. Some teenagers, however, may be uncomfortable with its insertion and the fact that the outer ring remains on the vulva during vaginal intercourse. Similar issues are encountered when considering the diaphragm as a contraceptive method for teenagers; therefore, it is not recommended as a first-line contraceptive method for most adolescents.

Sexually Transmitted Infections

All STIs should be managed according to the most recent guidelines published by the Centers for Disease Control and Prevention based on current epidemiology. See Chapter 60 for detailed discussion of the diagnosis and treatment of STIs in adolescents.

CASE RESOLUTION

A more detailed history should be obtained about the adolescent's menstrual history and daily activities (eg, With whom does she spend most of her time? What does she like to do in her spare time?). Additionally, the indications for a pelvic examination should be reviewed because most teenagers are not familiar with the new recommendations to delay the Pap smear until 21 years of age. Because the patient does not meet the new criteria for a Pap smear, the pelvic examination can be deferred. A discussion should follow about barrier and hormonal methods of contraception and their role in the prevention of pregnancy and STIs. Particular attention should be paid to the use of long-acting reversible contraceptives. Emergency contraception should also be reviewed with the patient. Written information as well as useful website addresses should be given to the adolescent for future reference. A follow-up visit should be scheduled for sometime in the next few months, especially if the patient decides to begin contraception.

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CHAPTER 59

Vaginitis

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CASE STUDY

An 11-year-old girl is brought to your office with vaginal itching for 1 week and a yellow discharge on her underwear for the past 4 days. The girl reports no associated abdominal pain, vomiting, or diarrhea. She has no urinary problems and denies any history of sexual abuse. Although she occasionally bathes with bubble bath, she most often takes showers. Except for the vaginal complaint, she is healthy, and she takes no medications.

The physical examination is notable for a soft, nontender abdomen with no organomegaly. Bowel sounds are audible in all quadrants. The genitalia are sexual maturity rating (ie, Tanner stage) 2. The labia majora and minora and the clitoris all appear normal, and the hymen is annular in shape with a smooth rim. A scant amount of yellow discharge, along with minimal perihymenal erythema, is noted at the vaginal introitus. The anal examination is normal, with an intact anal wink.

Questions

1. What are the most common causes of vaginal discharge in prepubescent girls? In pubescent girls?
2. What basic history-related information must be obtained from all females whose chief complaint is vaginal discharge?
3. What specific methods are used to perform a gynecologic examination in prepubescent girls? In pubescent girls?
4. What is the appropriate laboratory evaluation for prepubescent girls who complain of vaginal discharge? For pubescent girls? How does this evaluation differ for pubescent girls who are sexually active?
5. What are the various treatment options for girls with vaginitis?

Vaginal discharge is not an uncommon occurrence in prepubescent and pubescent girls. Primary care physicians are largely responsible for differentiating between a physiologic discharge, or leukorrhea, and a pathologic discharge, which occurs, for example, with a bacterial or yeast infection. In cases of an abnormal discharge, the possibility of sexual abuse must be considered and investigated appropriately (see Chapter 145). Primary care physicians should become familiar with the various causes of vaginal discharge in prepubescent and pubescent girls. More importantly, they should be comfortable performing age-appropriate gynecologic examinations in these patients so that the appropriate treatment can be initiated.

Vulvovaginitis, a term that often is used interchangeably with vaginitis or vulvitis, signifies inflammation of the perineal area, often accompanied by vaginal discharge. The discharge may be bloody, malodorous, or purulent, depending on the etiology (Table 59.1).

Epidemiology

Vulvovaginitis is a common gynecologic complaint in prepubescent girls. Most cases of vulvovaginitis in this age group result from nonspecific inflammation; vaginal cultures show normal flora in 33% to 85% of such cases. The incidence of more specific bacterial causes, such as group A β-hemolytic streptococcus, has been reported in approximately 10% to 20% of patients. Its occurrence seems to be seasonal, however, and confirming the diagnosis depends on the use of proper culturing techniques using the appropriate media. Other bacterial causes include respiratory pathogens, such as *Haemophilus influenzae, Neisseria meningitidis,* and *Streptococcus pneumoniae,* and enteric organisms, such as *Escherichia coli, Shigella*, and *Yersinia enterocolitica.* A positive culture for sexually transmitted pathogens such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae* is found in approximately 5% of children who are evaluated for child sexual abuse. Higher figures have been reported from select centers and when data from adolescent victims are included. These organisms are not considered part of the normal flora in prepubescent girls. Vaginal and rectal infections with *C trachomatis* can be acquired perinatally but usually are not considered perinatally acquired after 2 to 3 years of age.

Parasitic infections may also cause vaginal symptoms. Twenty percent of females with a rectal infestation of *Enterobius vermicularis,* the organism known as pinworm, have vulvovaginitis. Affected patients often complain of anal pruritus in addition to the vaginal discharge. Mycotic infections with organisms such as *Candida albicans* also can cause symptoms in prepubescent girls, although many of these girls have a previous history of recent oral antibiotic use, diabetes mellitus, immunosuppression, or other risk factors.

Clinical Presentation

Prepubescent and pubescent girls with vulvovaginitis most commonly present with a vaginal discharge, which may be white, purulent (ie, yellow or green), or serosanguineous. Consistency of the discharge can range from smooth and thin to thick and cottage

Table 59.1. Characteristics and Specific Causes of Vaginal Discharge

Color	*Consistency*	*Amount*	*Cause*
Clear/white	Thin	Variable	Physiologic leukorrhea; bacterial vaginosis
White	Cottage cheese–like	Moderate	*Candida*
White/yellow	Variable	Variable	Chemical irritation, pinworms, *Chlamydia trachomatis*, bacterial vaginosis
Yellow/green	Thick	Moderate–profuse	*Neisseria gonorrhoeae,* foreign body, *Trichomonas vaginalis,* group A β-hemolytic streptococci
Bloody	Variable	Variable	*Shigella,* group A β-hemolytic streptococci, foreign body

cheese-like. The discharge may also be malodorous. In addition, girls may complain of associated pruritus, erythema, urinary problems such as dysuria and increased frequency, and abdominal pain (Box 59.1). Sexually active pubescent girls with vaginitis from a sexually transmitted infection (STI) (eg, gonorrhea) generally have a more profuse, purulent discharge.

Pathophysiology

Prepubescent girls are at risk for developing vulvovaginitis for anatomic and physiologic reasons. Unlike pubertal girls and young adult women, prepubescent girls have no pubic hair and a smaller labial fat pad to protect the vaginal introitus. The labia minora are small and tend to open when girls are in a squatting position, thereby exposing the vaginal introitus. The relative proximity of the anus to the vagina in young girls also contributes to vaginal contamination with enteric organisms. More importantly, poor hygienic practices (ie, wiping back to front after urination or defecation) can further compound the problem.

In addition, the normal physiology of the vaginal epithelium in prepubescent girls predisposes to vaginitis and vulvar inflammation. The unestrogenized vaginal epithelium is relatively thin, immature, and easily traumatized. Additionally, unlike the acidic environment of the vagina in adult females, in prepubescent girls the pH of the vagina is neutral to alkaline, which allows overgrowth of pathogenic fecal and oropharyngeal bacteria. Local antibody production also may be lacking in the vagina of prepubescent girls. Vulvar skin is also easily irritated by harsh soaps, medications, chemicals such as bubble baths, and tight-fitting clothing or synthetic underwear. Girls who are overweight may be particularly susceptible to perineal irritation and subsequent inflammation of the area.

Box 59.1. Diagnosis of Vaginitis in Prepubescent and Pubescent Girls

- Nonphysiologic vaginal discharge
- Profuse, malodorous, or purulent vaginal discharge
- Perineal erythema
- Vaginal pruritus or irritation
- Dysuria

Differential Diagnosis

A vaginal discharge is normal at 2 distinct times in prepubescent girls: shortly after birth, secondary to the effects of maternal estrogen, and approximately 6 months to 1 year before the onset of menarche (physiologic leukorrhea), which occurs, in most girls, by sexual maturity rating (SMR) (ie, Tanner stage) 4. Other causes of vaginal discharge in prepubescent and pubescent girls are presented in Box 59.2.

Evaluation

Prepubescent Girls

History

A complete history should be obtained in all girls with a vaginal discharge (Box 59.3). Practitioners should inquire about the appearance of the discharge, its duration, and the relative amount. A profuse, purulent discharge is probably more consistent with 1 specific etiology (eg, *N gonorrhoeae*) than is a scant, thin discharge, which is suggestive of a nonspecific etiology. The existence of urinary problems also should be determined. Pooling of urine in the vagina secondary to labial fusion can result in vulvovaginitis in addition to a urinary tract infection. Changes in bowel or bladder habits and sudden changes in behavior, such as nightmares or inappropriate stranger anxiety, also should be noted. Such changes in behavior warrant a further inquiry into the possibility of sexual abuse, regardless of the practitioner's index of suspicion. Depending on the information disclosed and the age of the patient, a decision might be made to interview the child and parents or guardians independently. Other points to discuss include the type of detergents or soaps used for laundry as well as for bathing, because these may be irritating. Any recent illnesses also should be documented as a possible source of autoinoculation or, if oral antibiotics were prescribed, as a reason for the alteration of the normal vaginal flora. Additionally, patients' hygienic practices should be reviewed. Adolescent patients should always be interviewed alone (see Chapter 4). In particular, a confidential reproductive history must be obtained, keeping in mind that puberty and sexual activity alter normal vaginal flora.

Physical Examination

Although the genital examination is the priority, a complete physical examination should be performed. Doing so not only allows physicians to identify other abnormal physical findings, but also alleviates some

Box 59.2. Causes of Vaginal Discharge in Prepubescent and Pubescent Girls

Prepubescent Girls

- Estrogen withdrawal (neonates)
- Nonspecific vulvovaginitis
- Chemical irritation secondary to soaps and detergents
- Mechanical irritation from nylon panties or tight-fitting clothes
- Foreign body in vagina
- Poor hygiene
- Pinworms (*Enterobius vermicularis*)
- Yeast infection (eg, *Candida*)
- Bacterial infection (eg, group A β-hemolytic streptococcus, *Staphylococcus* species, nonencapsulated *Haemophilus influenzae, Escherichia coli, Shigella* species, *Salmonella* species, *Yersinia*)
- Sexually transmitted infection (eg, gonococcal infection, chlamydial infection, trichomoniasis, human herpesvirus, human papillomavirus)
- Congenital abnormality (eg, ectopic ureter [local inflammation])
- Acquired abnormality (eg, labial fusion [pooling of urine in vagina])
- Urethral prolapse
- Systemic illness (eg, scarlet fever, measles, varicella, Kawasaki disease, Crohn disease)
- Vulvar skin disease: lichen sclerosis, contact dermatitis, psoriasis, zinc deficiency

Pubescent Girls

- Physiologic leukorrhea
- Foreign body in vagina (eg, retained tampon or condom)
- Yeast infection (eg, *Candida)*
- Bacterial infection (eg, group A β-hemolytic streptococcus, *Staphylococcus aureus*)
- Sexually transmitted infection (eg, gonococcal infection, chlamydial infection, trichomoniasis, bacterial vaginosis)
- Chemical irritation (eg, douches, spermicides, latex [condoms])
- Local trauma (eg, penile or labial piercings)

Box 59.3. What to Ask

Vaginitis

Prepubescent Girl

- What is the color of the discharge?
- What is the consistency of the discharge?
- How profuse is the discharge?
- Is the discharge malodorous?
- How long has the discharge been present?
- How often does the discharge occur (ie, is it found on the panties daily)?
- Are there any associated problems (eg, dysuria, abdominal pain, enuresis, anal pruritus)?
- What types of laundry soap or detergent are used?
- Does the child take bubble baths?
- Has the child had any recent illnesses or treatment with oral antibiotics?
- Does the child clean herself after using the toilet, or does she require help?
- In what direction does she tend to wipe after a bowel movement?
- Is there a concern for, or history of, child sexual abuse?
- Has there been any recent behavioral changes (eg, nightmares, crying, recurrent abdominal pain)?
- What has the family done to manage the discharge?

Pubescent Girl (all of the above questions plus the following)

- What is the reproductive history (menstrual and sexual)?
- Does the adolescent douche or use scented panty liners?
- Does the adolescent use or share sex toys?
- Is there a history of sexual assault or abuse?
- If appropriate, is the adolescent using any form of barrier or hormonal contraception? When was the last episode of unprotected intercourse?
- How many sexual partners has the patient had?
- Does the patient or partner have any history of a previous sexually transmitted infection, including hepatitis B or C?

of the anxiety often associated with a genital examination. Because most vaginal discharges in prepubescent girls result from nonspecific vulvovaginitis, visualization of the cervix with a speculum is not indicated. Regardless of the sex of the examiner, a chaperone is required during the genital examination, particularly in postpubertal patients.

The overall demeanor of the young patient at the onset of the genital examination should be noted. Overly compliant, apathetic behavior in children may be a cause for concern for sexual abuse, especially in the context of a chronic or recurrent purulent vaginal discharge.

On physical examination, the patient's SMR must be noted and recorded. In addition, the external genitalia should be examined closely for the presence of any lesions or evidence of erythema. Chronic changes in labial skin, such as those associated with constant scratching, also should be documented.

Girls should be placed in the modified lithotomy or batrachian (ie, frog-leg) position, and the labia majora should be gently spread apart to visualize the hymen. The knee-chest position also can be used, depending on the comfort level of the practitioner and the patient. If the labia cannot be spread apart, the girl may have labial fusion or adhesions. Perihymenal and periurethral erythema should be noted, in addition to any evidence of edema, trauma, or abnormal masses such as urethral prolapse. Hymenal size and appearance should be carefully evaluated for any evidence of suspected sexual abuse (see Chapter 145). The appearance, consistency, and amount of the vaginal discharge, including the presence or absence of an odor, also should be documented. These findings may vary depending on the characteristics and cause of the discharge. Finally, the anus should be inspected for tone and any evidence of trauma or abnormal lesions such as genital warts. An anal wink is normally elicited. Although not usually indicated, a rectal examination should be performed to attempt to palpate a foreign body or mass in patients with chronic or bloody vaginal discharge. If the examiner cannot adequately visualize the perineum, vulva, and vaginal introitus using the batrachian or knee-chest position and the patient has persistent or significant symptoms, an examination under anesthesia may be warranted.

Laboratory Tests

Laboratory studies are often unnecessary in prepubescent girls with a nonspecific, non-bloody vaginal discharge, diffuse vulvar erythema, and no suspicion or history of sexual abuse. A vaginal culture for isolation of group A β-hemolytic streptococcus is indicated in girls with an abrupt onset of a serosanguineous discharge and a history of a systemic illness. The cellophane tape test may be helpful in diagnosing a pinworm infection in prepubescent girls with associated vulvar or anal pruritus. A potassium hydroxide (KOH) wet mount reveals pseudohyphae if a monilial infection is present; however, this diagnosis is often made clinically.

If the discharge is purulent, persistent, or malodorous or if sexual abuse is suspected, vaginal cultures must be obtained for *N gonorrhoeae* and *C trachomatis.* For suspected cases of sexual abuse or assault, culture remains the standard because of the risk of a false-positive result with nonamplified probe tests (eg, direct immunofluorescent smears, enzyme immunoassays) and nucleic acid amplification tests (NAATs). With genital and anal specimens, false-positive results can occur because of cross-reaction with fecal flora. In certain cases, a normal saline wet mount to check for mobile trichomonads may be indicated.

Pubescent Girls

History

In adolescent or pubescent girls with vaginal discharge, physicians should inquire about a history of sexual activity or assault in addition to other information that relates to their condition (see Box 59.3). Questions concerning the possible acquisition of an STI also must be asked in a nonjudgmental, confidential manner.

Physical Examination

Pubescent girls with an uncomplicated history who have never been sexually active should be examined in a similar fashion as the prepubescent female. The external genitalia should be examined to evaluate the SMR of the patient and the presence of any lesions or anatomic abnormalities, although SMR assignment may be challenging in the adolescent who has shaved her pubic hair. Perihymenal or periurethral erythema and hymenal size and appearance should be noted. In the absence of a mucopurulent or bloody discharge, a speculum examination is generally not warranted, particularly in the virginal adolescent.

In addition to an overall physical examination, a complete external genital and speculum examination is indicated in symptomatic, sexually active girls (ie, history of lower abdominal pain, severe dysmenorrhea, vaginal discharge). The purpose of the speculum examination is to visualize the cervix, properly obtain vaginal and cervical specimens, and examine the vagina for lesions (eg, condylomata acuminata). A bimanual examination also should be performed to check for cervical motion tenderness as well as adnexal masses or uterine tenderness, which are associated with pelvic inflammatory disease.

Laboratory Tests

For pubescent girls who are not sexually active, the laboratory evaluation should be similar to that described for prepubescent girls. Sexually active adolescents, however, warrant a more thorough evaluation to establish the etiology of their symptoms and investigate for cervicitis. Generally, if a speculum examination is being performed in these adolescents, a single-swab endocervical sample should be obtained and sent for gonorrhea and chlamydia via NAATs (eg, ligase chain reaction, polymerase chain reaction). Urine or a vaginal swab also should be sent for *N gonorrhoeae* and *C trachomatis* in those adolescents who refuse a pelvic examination or for screening purposes in the asymptomatic sexually active patient. Recommendations have changed for teenagers concerning the age at which cervical cancer screening (ie, Papanicolaou test) is indicated (see Chapter 58 for details). A culture or polymerase chain reaction test for herpes simplex is indicated only if the history of exposure is positive and ulcerative or vesicular lesions are present.

Other causes of vaginal symptoms can be determined by the pH and microscopic analysis of a fresh sample of the vaginal discharge. A normal saline wet mount should be made using a sterile, saline-moistened swab, especially if a nonspecific discharge is present or bacterial vaginosis (BV) is a concern. In addition, motile or static trichomonads may be seen on a wet mount as well as white blood cells, although a diagnosis of trichomonas should be made using NAAT on a vaginal, endocervical, or urine specimen. A 10% KOH mount is appropriate in cases of suspected candidiasis. Mixing 10% KOH with the discharge may also produce a "fishy" odor (ie, positive "whiff test"), which is consistent with BV and sometimes a trichomonad infection. Additionally, a vaginal pH greater than 4.5 is common with BV or trichomoniasis, although it is not specific. Commercial kits to evaluate for BV, trichomoniasis, and candida via nucleic acid probes are available for the office setting in which pH paper, KOH, and microscopic analysis of vaginal fluids is not possible. A Gram stain of any purulent material may result in an early diagnosis of gonococcal cervicitis. Serologies for syphilis also should be obtained in adolescents with suspected (ie, symptomatic) or proven STIs. In addition, these patients should be offered annual testing for HIV and syphilis.

Management

The goal of management of a nonspecific vaginal discharge is relief of the uncomfortable symptoms associated with this type of inflammation. Prepubescent girls should be instructed to discontinue use of all chemical irritants, including bubble baths and harsh soaps, in the genital area. The physician should recommend once or twice daily warm water sitz baths for approximately 1 week or until symptoms have improved. A small amount of vitamin A and D ointment or similar emollient can be used to protect the vulvar skin and promote healing. In addition, girls should be instructed in proper hygiene (eg, wiping front to back after a bowel movement, appropriate hand washing). The use of cotton or cotton-crotch underwear

and loose-fitting skirts or pants should be encouraged. Occasionally, a persistent, nonspecific vaginal discharge of more than 2 to 3 weeks' duration may benefit from a 10-day course of oral antibiotics such as amoxicillin, amoxicillin-clavulanate, or clindamycin. Girls with obesity and poor hygiene are especially prone to recurrences of vulvovaginitis.

Anticandidal medications, such as clotrimazole or miconazole cream, may be prescribed if a monilial infection is present. Empiric treatment with either of these medications may be warranted in children or adolescents with a previous history of oral antibiotic usage, diabetes mellitus, or other chronic conditions that may alter the normal vaginal flora.

Pinworms are treated with 2 oral doses of albendazole 400 mg, or pyrantel pamoate 11 mg/kg per dose (maximum dose, 1 g), with the second dose given 2 weeks after the first. Most authorities recommend repeat treatment after 2 weeks to kill worms that may have hatched after the first dose. All household contacts and caregivers of the infected person also should be treated with medication and instructed on good hand hygiene to prevent reinfection. Bedding and clothing should be laundered in hot water and dried in a dryer.

If a retained foreign body is suspected in a prepubescent girl, an examination under general anesthesia may be necessary. Alternatively, in a cooperative child practitioners can attempt vaginal irrigation by placing a small feeding tube at the hymenal opening and injecting warm saline. Toilet paper is the most commonly retrieved material in prepubescent girls.

Pubescent girls who are not sexually active should be treated in a similar fashion as prepubertal girls. If the discharge is consistent with a diagnosis of physiologic leukorrhea, practitioners should reassure patients and educate them about other issues related to puberty (eg, menarche, body odor). Sexually active adolescents with positive vaginal cultures, NAATs, or highly suspicious vaginal discharges should receive treatment depending on the suspected or causal organism (see Chapter 60 for details concerning treatment). Table 59.2 briefly outlines current treatment recommendations.

Any disclosure of molestation or assault by prepubescent or pubescent girls must be reported to the appropriate authorities. In addition, abnormal physical findings and positive cultures for STIs in prepubescent and pubescent girls who have never been sexually active must be reported to law enforcement and investigated.

Prognosis

In most prepubescent girls, vaginitis resolves spontaneously or after appropriate treatment with no permanent sequelae. In contrast, pubescent girls treated for vulvovaginitis or uncomplicated cervicitis from an STI continue to be at future risk for the development of pelvic inflammatory disease, HIV, and pregnancy because of their high-risk behavior, inconsistent use of barrier contraception (eg, condoms), and recurrent exposure to STIs.

Table 59.2. Treatment Recommendations for Adolescents With Infectious Vaginal Discharge

Organism	*Treatment*[a]
Neisseria gonorrhoeae	Ceftriaxone 250 mg intramuscularly once, *PLUS* azithromycin 1 g orally in a single dose
Chlamydia trachomatis[b]	Azithromycin 1 g orally once, or doxycycline orally 100 mg twice per day for 1 week
Trichomonas vaginalis	Metronidazole 2 g orally once, or tinidazole 2 g orally once
Bacterial vaginosis	Metronidazole 500 mg orally twice per day for 7 days; or metronidazole gel 0.75%, 1 applicatorful intravaginally once per day for 5 days; or clindamycin cream 2%, 1 applicatorful intravaginally at bedtime for 7 days[c]
Candida albicans	Over-the-counter intravaginal agents: 1% clotrimazole cream 5 g intravaginally for 7–14 days; 2% clotrimazole cream 5 g intravaginally for 3 days; 2% miconazole cream 5 g intravaginally for 7 days Prescription intravaginal agents: 4% miconazole cream 5 g intravaginally for 3 days; 0.4% terconazole cream 5 g intravaginally for 7 days; 0.8% terconazole cream 5 g intravaginally for 3 days; fluconazole 150 mg orally once

[a] For a complete list of treatment options, refer to Workowski KA, Bolan G; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR-3):1–137.

[b] May be associated with vaginal discharge, because it causes cervicitis.

[c] Oil-based product; thus, condom efficacy may be decreased during treatment.

CASE RESOLUTION

The girl and her parents should be assured that the discharge is consistent with a nonspecific inflammatory process. She should be instructed to take sitz baths for 1 week, discontinue bubble baths and the use of soap in the genital area, and wear loose-fitting clothes and cotton underwear. The girl should be reexamined in 1 to 2 weeks for resolution of her symptoms. No laboratory studies or medications are warranted at this time.

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CHAPTER 60

Sexually Transmitted Infections

Monica Sifuentes, MD

CASE STUDY

A 17-year-old boy presents with a small red lesion on the tip of his penis. He noticed an area of erythema a few weeks previously, but it resolved spontaneously. He reports no fever, myalgia, headache, dysuria, or urethral discharge. He is sexually active and only occasionally uses a condom. He did not use a condom during his last sexual encounter 2 weeks previously, however, because his partner uses oral contraception. The adolescent has never been treated for any sexually transmitted infection and is otherwise healthy. His partners are exclusively female.

On examination, he is a sexual maturity rating (ie, Tanner stage) 4 circumcised male with a 2- to 3-mm vesicle on the glans penis. Minimal erythema is present at the base of the lesion, and no urethral discharge is evident. The testicles are descended bilaterally, and no masses are palpable. Bilateral shotty, nontender, inguinal adenopathy is evident.

Questions

1. What conditions are associated with vesicles in the genital area?
2. What risk factors are associated with the acquisition of sexually transmitted infections during adolescence?
3. What screening tests should be performed in the patient with suspected sexually transmitted infection?
4. What recommendations about partners of the patient with sexually transmitted infection should be given?
5. What issues of confidentiality are important to address with the adolescent who seeks treatment for a sexually transmitted infection?

Many teenagers in the United States have their first sexual experience before they graduate from high school. In the 2017 national Youth Risk Behavior Surveillance System conducted by the Centers for Disease Control and Prevention (CDC), 40% of all students in high school reported having had sexual intercourse, with 3.4% of students nationwide reporting sexual intercourse for the first time before age 13 years. More important, nearly 12% of boys and 8% of girls in grades 9 to 12 reported having had 4 or more sexual partners during their life. The consequences of sexual activity in adolescents include increased rates of bacterial and viral sexually transmitted infections (STIs), unintended pregnancy, and the possible acquisition of long-term infections (eg, HIV) in the 15- to 24-year age group. Early detection and effective management of these infections, particularly HIV, can greatly enhance the teenager's current health and overall lifespan and reduce the risk of transmitting HIV to others. Because of the complex nature of these consequences, the physician must be skilled in and comfortable obtaining a complete sexual history in the adolescent patient and in diagnosing and managing common STIs and must refer individuals with more complicated infections to the appropriate subspecialists.

Increasing levels of risk-taking behaviors and sexual activity in adolescence directly affect STI trends in that patient population. Other influential factors include multiple sex partners, whether sequential or concurrent; inconsistent and incorrect use of condoms; unprotected sex; experimentation with drugs, including alcohol, which results in poor judgment concerning sexual activity; mental health issues; poor adherence to antibiotic regimens; and biologic factors, such as young age at onset of menarche and the presence of cervical ectopy in adolescent females. The feeling of invulnerability and the desire for autonomy that occur commonly during adolescence make most sexual encounters spontaneous rather than premeditated. As a result, preventive measures are forgotten, ignored, or overlooked by individuals of this age group, and the short- and long-term consequences of their actions are seldom considered. Other factors that influence STI trends are related to societal norms. Traditionally, unlike in other industrialized countries, educational materials and STI services have not been readily available to adolescents in some areas of the United States. Many teenagers also have difficulty accessing comprehensive health care in their communities and are concerned about confidentiality when obtaining medical services for sensitive issues. Additionally, the depiction of casual sexual relationships in the media, music videos, and motion pictures may contribute to the glamorization of sex. Advances in technology via unlimited internet access also give teenagers the opportunity to communicate with peers who were previously unreachable and to access health information that is unfiltered and may be misleading.

Epidemiology

The overall prevalence of STIs in adolescents is difficult to estimate because not all STIs are reportable, many infections are asymptomatic, and collected data may not include specific subsets of the population. It has been estimated, however, that more than 50% of all new STIs diagnosed annually in the United States occur among teenagers and young adults aged 15 to 24 years. After human papillomavirus (HPV), *Chlamydia trachomatis* is the second most common STI in the United States. *Chlamydia trachomatis* remains the most common cause of cervicitis and urethritis in adolescents, with age-specific rates highest among girls and young women 15 to 24 years of age and young men 20 to 24 years of age. Additionally, studies have shown that certain adolescent subpopulations are at increased risk for chlamydial infection, such as homeless and incarcerated youth, socioeconomically disadvantaged youth, ethnic minority youth, teenagers attending family planning clinics, and pregnant adolescents. Complications of unmanaged chlamydial cervicitis occur in 10% to 15% of cases and include pelvic inflammatory disease (PID), ectopic pregnancy, chronic pelvic pain, and infertility. Epididymitis, a result of urethral infection, occurs in 1% to 3% of infected males. Other conditions that may occur in males engaging in receptive intercourse include proctitis, proctocolitis, and reactive arthritis (formerly known as Reiter syndrome).

In 2017, the CDC reported gonorrhea rates to be highest among adolescents and young adults compared with the general population, particularly among teenage girls and young women. The highest rates of gonorrhea reportedly occur in adolescent females, young men in their early 20s, young ethnic minority adults living in the inner city, incarcerated youth, men who have sex with men, and commercial sex workers. Injection drug use, exposure to commercial sex workers, and numerous sexual contacts also contribute to the risk of infection. The prevalence of gonorrhea in 15- to 19-year-old girls and young women was 557 per 100,000 population. Boys and young men 15 to 19 years of age had the second highest rates of gonorrhea (323 per 100,000) compared with men age 20 to 24 years, who had even higher rates of gonorrhea (705 per 100,000). Of the more than 1 million cases of PID reported annually in the United States, approximately 20% occur in sexually active adolescents. The risk of developing PID is increased several fold in this age group compared with adult women for several reasons: failure to use condoms consistently, multiple new partners within the previous 12 months, and a history of other STIs. Additionally, according to the National Survey of Family Growth conducted by the CDC, girls who initiated vaginal intercourse at younger than 15 years had the highest prevalence of PID. Complications of PID, such as tubo-ovarian abscess (TOA) formation, are more likely to occur in adolescents as a result of late presentation, delayed diagnosis, difficulty accessing health care, and nonadherence with prescribed treatment regimens.

Although the rate of primary and secondary syphilis declined from 1990 to 2000, the number of cases has since been increasing at epidemic proportions, primarily among young men of color who have sex with men. During 2005, the incidence of syphilis was highest among women in the 20- to 24-year-old age group and among men in their mid-30s. In 2017, however, young men age 20 to 24 years had the highest rates of syphilis. Studies have shown that people with syphilis, as well as other STIs that cause genital ulcers, also are at increased risk for HIV acquisition.

Human papillomavirus is the most common STI in the United States, with the highest infection rates among adolescents and young adults. Recent studies report a prevalence in sexually active adolescents ranging from 30% to 60%, with one-half of new infections occurring in individuals 15 to 24 years of age. The prevalence of HPV in adolescents varies widely for 2 reasons: infection with HPV is often latent and generally regresses spontaneously, particularly in young adolescents, and HPV is not a reportable condition. Behavioral and biological risk factors for HPV infection have been identified and include early age of sexual initiation, unprotected intercourse with multiple sexual partners, the partner's number of sexual partners, a lack of consistent condom use, and a history of another STI, such as genital herpes, which may facilitate HPV acquisition by compromising mucosal integrity. Cigarette use also increases the risk of infection and HPV-related disease, as does an altered immune system.

Infection with herpes simplex virus (HSV-1 and HSV-2) is underestimated and is the most common cause of genital ulcerative disease in the United States. Most primary episodes in adolescent females and young men who have sex with men are caused by HSV-1 and recurrent infections by HSV-2.

As of 2016, 21% of all new HIV diagnoses in the United States were among youth. According to the CDC, most of those new diagnoses occurred among young gay and bisexual men, particularly young black/African American and Hispanic/Latino gay and bisexual men. Because the time from acute HIV infection to immunosuppression is, on average, 10 years for untreated adolescents, estimates of asymptomatic or early HIV infection often are based on reported cases of AIDS in young adults in their third decade. Most of these individuals are infected through sexual contact or injection drug use. Teenage subpopulations who are at particularly high risk for acquiring HIV are youth who have male-to-male sexual contact; are transgender; are experiencing homelessness or who have run away; are users of injection drugs; are incarcerated; are in the foster care system; or have been sexually or physically abused. Of note, research has shown that young gay men who have sex with older partners are at increased risk for HIV infection because the older partner is more likely to have had more sexual partners and therefore has an increased likelihood of being infected with HIV.

Clinical Presentation

The adolescent with an STI may consult his, her, or their physician with specific complaints related to the genitourinary system, such as painful urination or vaginal discharge. The adolescent also may report more generalized complaints, such as fever, rash, and malaise, especially in cases of primary HSV-1 and HSV-2 infection or during the viremic phase of HIV acquisition (Box 60.1). Additionally, some teenagers use a vague complaint as an opportunity to visit their primary care physician with the hope that the physician will inquire

Box 60.1. Diagnosis of Sexually Transmitted Infection

Males

- Dysuria
- Urethral discharge or pain
- Testicular pain
- Presence of any lesions in the genital area, such as ulcers, vesicles, or warts
- Nonspecific rash
- Sexual partner who has a sexually transmitted infection

Females

- Dysuria
- Abnormal vaginal discharge
- Intermenstrual or irregular vaginal bleeding
- Dysmenorrhea
- Dyspareunia
- Postcoital bleeding
- Lower abdominal pain
- Nonspecific rash
- Systemic symptoms, such as fever, nausea, vomiting, or malaise
- Presence of any lesions in the genital area, such as ulcers, vesicles, or warts
- Sexual partner who has a sexually transmitted infection

about sexual behaviors. The likelihood that the adolescent will disclose his, her, or their true concern about an undiagnosed infection is greatly increased if the physician appears genuinely interested and nonjudgmental.

Pathophysiology

Several biologic factors contribute to the increased prevalence of STIs in adolescents, particularly in females. At the onset of puberty, the columnar epithelial cells in the vagina transform to squamous epithelium, while columnar cells at the cervix persist (Figure 60.1). With increasing age, the squamocolumnar junction recedes into the endocervix. In adolescent females, however, this junction, referred to as cervical ectopy, often is located at the vaginal portion of the cervix and is relatively exposed, which places these individuals at particular risk for gonococcal and chlamydial infections. The infectious organisms preferentially attach to cervical columnar cells and infect them. The use of oral contraceptives prolongs this immature histologic state.

The cytologic changes observed in cervical cells of adolescents with HPV infection are also believed to be age-related. The immature cervical metaplastic or columnar cells seem to be more vulnerable to infection and neoplastic changes. Additionally, exposure to other cofactors (eg, tobacco use, multiple episodes of new HPV infection) is likely to promote the development of squamous intraepithelial neoplasia and cervical carcinoma. Not all young women exposed to

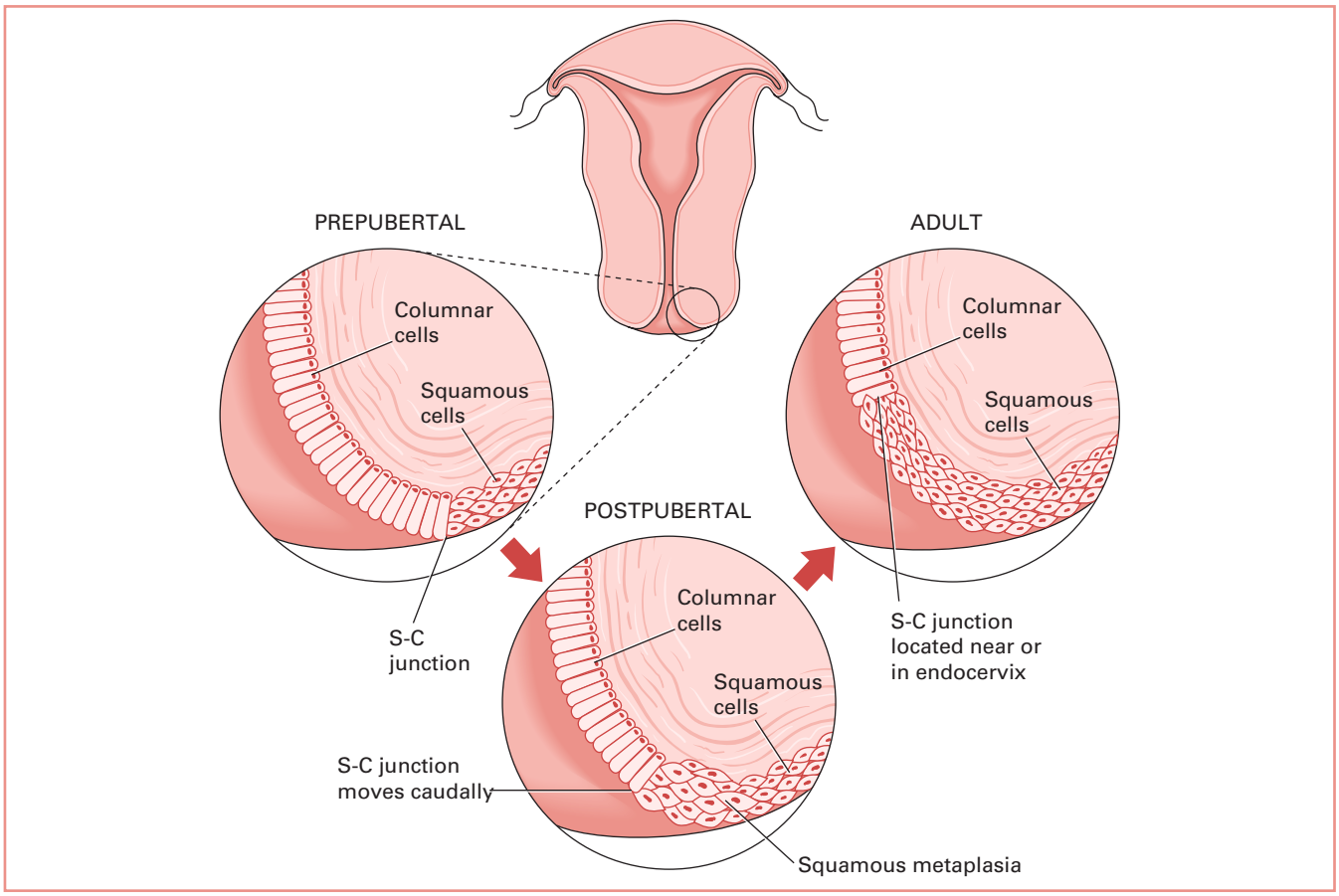

Figure 60.1. Development of the cervical squamocolumnar (S-C) junction, from puberty to adulthood.

HPV develop lesions or progress to squamous intraepithelial neoplasia, however, and most do not remain positive for HPV throughout their lifetime.

The presence of genital ulcers has been shown to facilitate the transmission and acquisition of HIV. Such ulcers provide a point of entry past denuded epithelium. Additionally, it is hypothesized that many activated lymphocytes and macrophages are located at the base of the ulcer and are therefore susceptible to infection by HIV.

Pelvic inflammatory disease usually manifests from an ascending mixed polymicrobial infection, often related to an untreated STI of the cervix and vagina. The infection spreads contiguously upward to the upper genital tract, resulting in inflammation involving the endometrium, fallopian tubes, and/or ovaries. The most common causal organisms, which account for more than one-half of the cases of PID in most series, are *C trachomatis* and *Neisseria gonorrhoeae.* Other organisms include *Escherichia coli,* other enteric flora, and microbes implicated in bacterial vaginosis, such as *Mycoplasma hominis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Bacteroides* species, and anaerobic cocci. Viruses such as HIV and HSV-1 and HSV-2 can facilitate the process of this ascending infection by disrupting normal immunologic barriers to infection, such as altering the vaginal pH and flora and the cervical mucus barrier.

Differential Diagnosis

Most patients with STIs present with 1 of 5 clinical syndromes: urethritis/cervicitis, epididymitis, PID, genital ulcer disease, or genital warts, all of which are easily diagnosed with the appropriate diagnostic studies (Box 60.2). Other conditions that mimic STIs must be considered, however, particularly in certain cases in which the adolescent denies sexual activity or in which the disorder does not respond to routine medical management. These disorders include mucocutaneous ulcers associated with systemic lupus erythematosus and Behçet syndrome. Often, systemic disorders such as these can be ruled out based on the history, although a minimal workup may be necessary. Benign oral lesions, such as aphthous ulcers, also can be confused with herpetic ulcers. When evaluating an adolescent female with acute lower abdominal pain, it is necessary to rule out surgical conditions such as appendicitis, ovarian torsion, and ectopic pregnancy. In the sexually active male with testicular pain, testicular torsion must be cautiously considered and thoroughly evaluated before a diagnosis of acute epididymitis is made.

Box 60.2. Differential Diagnosis of Sexually Transmitted Infection by Clinical Syndrome

Urethritis
- *Neisseria gonorrhoeae*
- Nongonococcal disease
  - *Chlamydia trachomatis*
  - *Ureaplasma urealyticum*
  - *Trichomonas vaginalis*
  - *Mycoplasma genitalium*
  - Herpes simplex (HSV-1 and HSV-2) virus
  - *Yeasts*

Cervicitis
- *C trachomatis*
- *N gonorrhoeae*
- *T vaginalis*
- *M genitalium*
- HSV (primarily HSV-2)

Pelvic Inflammatory Disease
- *N gonorrhoeae*
- *C trachomatis*
- Anaerobes
- Gram-negative rods
- Streptococci
- *Mycoplasma hominis*
- *M genitalium*
- *U urealyticum*

Vaginitis
- *T vaginalis*
- *Candida albicans* and other yeast
- *Gardnerella vaginalis*

Genital Ulcers
- *Treponema pallidum* (syphilis)
- HSV-1 and HSV-2
- *Haemophilus ducreyi* (chancroid)
- *C trachomatis* (lymphogranuloma venereum)
- Epstein-Barr virus (infectious mononucleosis)

Genital Warts
- *T pallidum* (condyloma latum)
- Human papillomavirus (condyloma acuminata)

Proctitis
- *N gonorrhoeae*
- *C trachomatis*
- *T pallidum*
- HSV-1 and HSV-2
- Particular to youth who engage in same-sex sexual activity (in addition to the above)
- Hepatitis A and B virus
- *Shigella*
- *Campylobacter*
- *Giardia lamblia*
- *Entamoeba histolytica*

Pharyngitis
- *N gonorrhoeae*
- HSV-1 and HSV-2

Evaluation

In all sexually active adolescents, a complete medical and psychosocial history, including a sexual history, should be obtained confidentially (Box 60.3). The risk assessment for an STI, particularly HIV, should be based on a review of actual sexual behaviors rather than on an adolescent's stated sexual orientation at the time of the visit. A detailed gynecologic history also should be reviewed with females, including any recent changes in menstrual bleeding and dyspareunia. The remainder of the history should focus on the patient's specific complaint and any associated symptoms. A complete physical examination, including a thorough genital examination, should be performed. Although diagnostic tests are determined based on findings from the history and physical examination, it is important to remember that many adolescent patients are asymptomatic, and screening for common STIs, such as chlamydia and gonorrhea, should be performed at least annually on all sexually active teenagers through noninvasive urine or vaginal nucleic acid amplification testing (NAAT). Adolescents at increased risk for STI (eg, a history of STIs, multiple partners, young men who have sex with men) should be screened every 6 months or more frequently depending on their risk factors or current symptomatology.

Urethritis and Epididymitis

History

Because infectious urethritis is more common in young men than in older men, all sexually active adolescent males should be asked about the presence of dysuria, urethral discharge, and urethral erythema or pruritus. In females, symptoms such as dysuria and increased urination may have a more gradual onset and are reported more frequently than other symptoms, such as meatal edema, erythema, or urethral discharge, which are rarely noticed in girls. General urinary symptoms, such as acute urinary frequency and urgency, are uncommon with urethritis, especially in males. More often, urethritis is asymptomatic, and the diagnosis is made by routine annual screening in sexually active adolescents or through known contact with a partner with an STI (eg, *C trachomatis, N gonorrhoeae*).

To diagnose acute epididymitis, the sexually active male should be asked about testicular pain and swelling. Symptoms associated with urethritis also may be present or may have preceded the scrotal symptoms.

Box 60.3. What to Ask

Sexually Transmitted Infections

- Are you currently in a relationship?
- Are you sexually active? Do you have or have you had oral, vaginal, and/or anal intercourse?
- At what age did you begin to have sex?
- Do you have sex with men, women, or both?
- How many partners have you had? When was your last contact?
- Have you ever been forced to have sex, had sex while under the influence of alcohol or drugs, or exchanged sex for food, shelter, money, or drugs?
- Do you or your partner(s) use contraception? What type?
- Do you or your partner(s) use drugs or alcohol?
- Have you or any of your sexual contacts ever been diagnosed with a sexually transmitted infection? Did you and they undergo treatment?
- Do you have abdominal pain, dysuria, increased urinary frequency, or hesitancy?
- Have you noticed any ulcers, blisters, warts, or other bumps in the genital area? Are the lesions painful?
- Have you had any recent systemic symptoms, such as fever, chills, body aches, sore throat, or rashes?
- For females: Do you have a vaginal discharge or itching? Is sex uncomfortable or painful? Do you have bleeding between periods or after intercourse?
- For males: Do you have a discharge from your penis? Any testicular pain or swelling? Any associated burning or itching?

Physical Examination

The genital examination in both males and females must be performed in the presence of a chaperone, regardless of the sex of the health professional.

In males, the presence of a urethral discharge and its consistency (ie, mucopurulent or purulent) should be noted. Any other urethral or genital lesions also should be assessed. The epididymis, spermatic cord, and testes should be palpated carefully for tenderness and swelling.

In symptomatic females, a full pelvic examination should be performed after careful examination of the external genitalia for any ulcerative or wart-like lesions. The urethra should be inspected for edema, erythema, or any evidence of a discharge prior to insertion of the speculum. Urethritis is most often caused by *C trachomatis,* but HSV-1 and HSV-2 and trichomoniasis can also cause urethritis. The presence or absence of a vaginal or endocervical discharge also should be noted during the pelvic examination; however, its absence does not rule out the possibility of an STI.

Laboratory Tests

Screening tests using urine or vaginal samples are considered standard of care for detecting gonorrhea and chlamydia, especially in the asymptomatic sexually active adolescent. These nonculture tests rely on amplification of DNA (ie, polymerase chain reaction [PCR], ligase chain reaction) and are highly sensitive and convenient for screening teenagers because the test can be performed on a routine patient-obtained urine or a physician- or patient-obtained vaginal specimen. A disadvantage is that these tests may have an increased potential for false-positive results, making a definitive diagnosis questionable in a judicial setting (eg, child sexual abuse). In the adolescent population, however, NAATs definitely are more acceptable than tests requiring a direct urethral swab specimen and should be used to confirm chlamydial or gonococcal urethritis for screening or diagnostic purposes. In cases of persistent symptoms or recurrent urethritis, particularly in males, infection with *M genitalium* should be considered. Testing for this organism is not currently available in most laboratories, however.

Color duplex Doppler ultrasonography may be necessary to differentiate between epididymitis and testicular torsion in the adolescent male. Whether the diagnosis of testicular torsion is questionable or confirmed, an immediate urologic consultation is necessary.

Cervicitis

History

Cervicitis in females is parallel to urethritis in males. Because cervicitis is a local infection, systemic symptoms may not occur, which makes asymptomatic infections, especially with *C trachomatis,* quite common. A variety of important points related to the patient history and associated complaints should be addressed with all sexually active female teenagers to rule out other etiologies, however. The physician should ask questions such as, "Do you have a vaginal discharge?"; "What color is the discharge?"; "Is there any odor?"; "Are you experiencing any urinary frequency, urgency, or dysuria?"; and "Have you had any nonmenstrual vaginal bleeding or spotting, including postcoital bleeding or dyspareunia?" A known exposure to other STIs must be ascertained as well, which can be discerned with questions such as, "Is your current partner symptomatic or receiving antibiotic treatment?"; and "Do you or your current or any past partner have a history of an STI?"

More generalized symptoms, such as moderate lower abdominal pain (acute or chronic) associated with nausea, vomiting, and fever, may be indicative of a complication of untreated or undetected cervicitis, such as PID. Additional symptoms associated with disseminated gonococcal infection, such as fever, arthritis, and rash, should be investigated as well as the involvement of other areas of the body (eg, sore throat).

Physical Examination

After completing the full physical examination, with particular attention paid to the patient's skin, pharynx, hands, fingers, and joints, the physician should focus on the genitourinary examination. In the presence of a chaperone, the sexual maturity rating should be noted first, and the external genitalia should be examined for the presence of any lesions or inflammation of the perineum. Any urethral erythema or discharge also should be noted. The presence of a vaginal discharge can be assessed more completely when performing the speculum examination, which should be considered in all sexually active adolescent females with vaginal or persistent lower urinary tract complaints.

During the speculum examination, the vaginal mucosa should be inspected, the presence of a vaginal discharge identified, and the appearance of the cervical os documented. The physician should determine whether a purulent or mucopurulent exudate is coming from the endocervix and look for any evidence of cervical friability or sustained endocervical bleeding as a swab is gently passed through the cervical os to perform the NAAT. A cotton swab of the vaginal discharge should be collected for a microscopic evaluation of wet preparations (wet mount), if necessary. Cervical inflammation must be differentiated from normal adolescent cervical ectopy. A presumptive diagnosis of mucopurulent cervicitis is made in the setting of copious discharge from the cervical os, cervical erosion, or friability. A bimanual examination also must be performed to evaluate for cervical motion tenderness (CMT), adnexal masses or fullness, and uterine tenderness.

Laboratory Tests

According to the CDC, NAATs for *N gonorrhoeae* and *C trachomatis* are preferred for the diagnostic evaluation of cervicitis and can be performed on vaginal, urine, or endocervical specimens. If a pelvic examination is being performed, an endocervical or vaginal swab specimen for NAATs can be collected by direct visualization. A wet mount evaluation to diagnose associated STIs (eg, trichomoniasis) is recommended, especially if the discharge is foul smelling or frothy; however, immediate specimen evaluation is required for optimal results. Alternative diagnostic tests for trichomoniasis are also available for females; vaginal, endocervical, or urine specimens can be tested using NAAT. The adolescent who is diagnosed with a new STI or engaged in other high-risk behaviors, such as unprotected sexual intercourse, multiple sexual partners, inconsistent or incorrect condom use, or young men who have sex with men, should undergo testing for other STIs as well, such as HIV, syphilis, and viral hepatitis.

Pelvic Inflammatory Disease

History

When considering a diagnosis of PID, the history should include a discussion of known risk factors, such as unprotected sexual activity; the number of sexual partners, especially new partners in the previous 2 months; a previous history of an STI or recent exposure to an STI; the type and consistency of contraceptive use; and the timing of the last menstrual cycle, because many young women present with PID during the first half of their menstrual cycle. The physician also should inquire about other symptoms that are often associated with PID: the onset, duration, quality, and location of abdominal pain; urinary symptoms that may be indicative of concomitant urethritis; intramenstrual bleeding; dysmenorrhea or dyspareunia; abnormal vaginal discharge; right upper quadrant pain; and systemic symptoms, such as nausea, vomiting, fever, and malaise. The classic symptoms of PID, which include pelvic or lower abdominal pain, vaginal discharge, fever, and abnormal bleeding, are not always present. More often, symptoms are nonspecific or vague, and the physician must maintain a high index of suspicion in any sexually active female with acute or subacute pelvic or lower abdominal pain.

Physical Examination

Classic signs of acute PID include fever with lower abdominal pain and tenderness of the cervix, uterus, or adnexa on bimanual examination. The clinical presentation can vary from vague discomfort to severe pain, however, depending on the particular patient. Therefore, before performing the pelvic examination a thorough physical examination should be completed to exclude other common causes of lower abdominal pain. This should include a review of the vital signs, evaluating for fever or tachycardia. The blood pressure also

must be reviewed carefully because hypotension can occur with a ruptured ectopic pregnancy, which may present with similar symptoms, including abdominal pain and vaginal bleeding. The abdomen should be assessed for tenderness and guarding. The location of the pain is particularly relevant because certain acute surgical conditions, such as appendicitis, ovarian torsion, and ectopic pregnancy, are important considerations in the differential diagnosis of PID. Additionally, right upper quadrant pain is consistent with perihepatitis (ie, Fitz-Hugh–Curtis syndrome), which can occur with a gonorrheal or chlamydial infection. In the presence of a chaperone, the speculum examination should be performed, looking for a mucopurulent endocervical exudate or any evidence of cervicitis (eg, cervical friability or erosion). The cervix should be carefully palpated for any evidence of CMT and the uterus for tenderness or adnexal masses on bimanual examination.

Laboratory Tests

The diagnosis of PID is based on clinical findings and a high index of suspicion, after other causes for pelvic or lower abdominal pain have been excluded. Previous CDC criteria for the diagnosis of PID included 3 major components: lower abdominal pain, CMT, and adnexal tenderness. Current recommendations outline 1 or more minimum clinical criteria and 5 additional criteria to support the diagnosis (Box 60.4). Particularly when evaluating an adolescent for PID, early conservative treatment and maximum sensitivity for subtle clinical findings are paramount to avoid a delayed or missed diagnosis. A NAAT for *N gonorrhoeae* and *C trachomatis* should be sent on the endocervical or vaginal swab specimen obtained during the pelvic examination.

Other laboratory studies to obtain include a complete blood cell count with differential and a sedimentation rate or C-reactive protein level, although in some cases the laboratory tests are normal. A urine pregnancy test should be performed to exclude the possibility of a concomitant intrauterine or ectopic pregnancy. Additionally, a urinalysis and urine culture should be obtained in the patient who reports dysuria. A serologic test for syphilis and HIV testing also should be offered to the adolescent. Testing for viral hepatitis is recommended in the patient who has not been immunized against hepatitis B or who has exposure to injection drug use, thereby placing the patient at risk for hepatitis C.

Laparoscopy may be performed to make a definitive diagnosis of PID or to obtain cultures directly from the fallopian tubes in cases in which the diagnosis is equivocal or the patient is not improving on standard antimicrobial therapy. Immediate consultation with a gynecologist is necessary for these challenging cases.

Imaging Studies

Transvaginal ultrasonography may help exclude diagnoses such as ectopic pregnancy or ovarian torsion and can aid in the detection of complications associated with PID, such as TOA. Fluid in the cul-de-sac may be evident on ultrasonography; however, it is not specific for the diagnosis of PID.

Box 60.4. Diagnosis of Pelvic Inflammatory Disease

Pelvic or Lower Abdominal Pain and ≥1 of the Following Minimum Criteria on Pelvic Examination

- Cervical motion tenderness
- Uterine tenderness
- Adnexal tenderness

Additional Findings

- Oral temperature >38.3°C (>101°F)
- Abnormal cervical mucopurulent discharge or cervical friability
- Presence of abundant numbers of white blood cells on saline microscopy of vaginal fluid
- Elevated erythrocyte sedimentation rate or C-reactive protein level
- Laboratory documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*

Specific Criteria for the Diagnosis

- Inflammatory tubal mass or tubo-ovarian complex seen on magnetic resonance imaging or transvaginal ultrasonography, or evidence of pelvic infection (ie, tubal hyperemia) on Doppler ultrasonography
- Histologic evidence of endometritis on endometrial biopsy
- Laparoscopic abnormalities consistent with pelvic inflammatory disease

Derived from Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR-3):1–137.

Genital Ulcers

History

Likely the most important information to obtain from the adolescent with genital ulcers is whether the ulcers are painful. A painless chancre on the penis in males, around the mouth, in the oropharynx, or in females on the external genitalia is consistent with primary and secondary syphilis. If the lesions are painful or are associated with a grouped vesicular eruption, HSV-1 and HSV-2 is the likely cause. The presence of systemic symptoms, such as fever, chills, headache, or malaise, also is important to discern because these symptoms can occur with a primary infection with HSV-1 and HSV-2 or secondary syphilis. Generalized complaints, however, are associated with secondary syphilis in only 50% of cases. A history of adenopathy, whether localized or generalized, also must be noted, along with dysuria, which may be present in females with HSV-1 and HSV-2. Additionally, a history of a viral-like illness accompanied by a rash warrants further investigation because a diffuse maculopapular rash, especially on the palms and soles, is a classic sign of secondary syphilis. Because a nonspecific rash also can occur with primary HIV infection, all possible exposures to other STIs should be reviewed with the teenager.

Physical Examination

All adolescents who present with chancres, or ulcers, should undergo a complete physical examination. The skin, including the palms and soles, should be examined closely for any dull red to reddish-brown macular

or papular lesions. The oropharynx should be carefully checked for chancres or blisters. All lymph nodes should be palpated for pain, enlargement, or induration. Suppurative or fluctuant nodes often are associated with chancroid caused by *Haemophilus ducreyi*. The genital examination should focus on the appearance of the lesions, with the following questions in mind: Are the lesions ulcerative, clustered, and painful (ie, HSV-1, HSV-2, or chancroid)? Are they associated with grouped vesicles on an erythematous base (ie, HSV-1 or HSV-2)? Is tender inguinal adenopathy present (ie, HSV-1, HSV-2, or chancroid)? Or does the patient have a single, painless, indurated chancre with a clean base and a sharply defined, slightly elevated border (ie, syphilis)? The lymph nodes associated with this syphilitic type chancre often are nontender but enlarged. Other less common STIs produce genital ulcers that often are painful and deep and may be accompanied by some purulence. Adenopathy can be quite impressive with chancroid and lymphogranuloma venereum, as in the case of *C trachomatis*.

Laboratory Tests

The necessary diagnostic tests depend on the patient's clinical picture. However, all adolescents who present with a painless ulcerative lesion should undergo dark-field microscopy for syphilis or direct fluorescent antibody testing of the lesions, which is also available and quite specific. Nontreponemal serologic tests for syphilis, such as the Venereal Disease Research Laboratories (VDRL) or rapid plasma reagin (RPR) tests, should be done if direct examination is not available or the clinical appearance of the ulcer is nonspecific. In cases of early primary syphilis in which the VDRL or RPR may not be reactive initially, the test should be repeated in 1 week. Treponemal tests, such as the fluorescent treponemal antibody absorption test, should be used only as confirmatory tests and not for screening purposes. The physician must keep in mind that false-positive nontreponemal testing can occur in some clinical conditions, such as pregnancy, autoimmune disease, and HIV. In these instances, confirmatory treponemal testing is required.

Viral cell culture and PCR are the preferred diagnostic tests for individuals who seek treatment for painful genital ulcers or other mucocutaneous lesions likely caused by HSV-1 and HSV-2. Samples should be obtained from the base of a fresh unroofed vesicle. Herpes simplex virus-1 or HSV-2 serology for HSV-1 and HSV-2 is generally not helpful.

Because of the well-described correlation between genital ulcers and HIV, it is recommended that all patients with a diagnosis of syphilis be tested for HIV as well. Conversely, annual syphilis screening is not indicated for all teenagers but is currently recommended for the adolescent with multiple sexual partners; a history of injection drug use; a history of a male having sex with males; or a previously diagnosed STI. Additionally, the seroprevalence of syphilis in the health professional's particular community or specific patient population should be taken into account when contemplating more frequent screening.

Genital Warts

History

Risk factors for HPV infection should be assessed in all sexually active adolescents regardless of their immunization status. These factors include a history of multiple sexual partners, age younger than 25 years, a previous history of STIs, lack of consistent condom use, pregnancy, altered immune response, and tobacco use. Symptoms may include pruritus, pain, or dyspareunia, but often the condition is asymptomatic. The adolescent may palpate a lesion on the external genitalia, report local irritation, or note bleeding from larger, traumatized lesions, depending on lesion location.

Physical Examination

A complete pelvic examination should be performed on all sexually active female adolescents who report lower abdominal pain, vaginal discharge, or intramenstrual or postcoital vaginal bleeding, or who express concern with "something they felt" in the genital area. Before the speculum is inserted, the external genitalia should be carefully inspected for lesions. Genital warts (ie, condylomata acuminata) most commonly appear on squamous epithelium as irregular polypoid masses with an irregular, cauliflower-like surface that may coalesce into larger lesions. Usually these are located at the posterior introitus, labia minora, and the vestibule in females; they may be found on the cervix and in the vagina as well.

In males, warts are found more commonly on the circumcised penile shaft, glans, or corona, as well as under the foreskin of the uncircumcised penis. They also may appear as flat, flesh-colored papules on the scrotum and anus. Because the anus is a common location for lesions, it should be inspected carefully in males and females. Intra-anal warts are seen in persons who have receptive anal intercourse, but they also can occur in men and women with no history of anal sexual contact. *Condylomata plana* are subclinical lesions that are not grossly visible but are apparent on colposcopy and histology.

Condylomata lata are flat, flesh-colored warts that occur in moist areas (ie, anus, scrotum, vulva) and may be associated with other signs of secondary syphilis.

Laboratory Tests

The diagnosis of genital warts often is made by visual inspection and generally does not require confirmation by biopsy. A biopsy may be required in specific instances, however, such as with an uncertain diagnosis, in the case of a lesion that is not improving or that worsens with standard therapy, for an atypical lesion, in the immunocompromised patient, or for warts that appear pigmented, indurated, bleeding, or ulcerated. A definitive diagnosis of HPV infection is based on detection of viral nucleic acid or capsid protein. Tests that detect specific types of HPV DNA are available but are not routinely recommended because this information does not alter the clinical management of the condition, except in extraordinary circumstances.

Historically, suspicious areas of white epithelium identified by the application of 3% to 5% acetic acid or a specific vascular pattern consistent with HPV infection were biopsied. This procedure is no

longer recommended, however, because prospective studies have shown that many cervical and anogenital squamous intraepithelial lesions in adolescents resolve spontaneously if left untreated. For this reason, the American College of Obstetricians and Gynecologists and the American Cancer Society currently recommend that routine screening for cervical cancer should be performed starting at 21 years of age. Cervical Papanicolaou testing is no longer recommended by any major medical organization for individuals younger than 21 years, with the exception of adolescents with HIV infection, for whom screening is warranted 1 year after onset of sexual activity because of the high rate of progression of abnormal cytology.

All teenagers should be offered STI screening. Nucleic acid amplification tests for the detection of gonorrhea or chlamydia can be performed on urine, endocervical, or vaginal specimens. Additionally, a serum nontreponemal antibody test for syphilis (RPR or VDRL) is indicated. An HIV antibody test should be offered to all adolescents who are deemed at risk.

A urinalysis for asymptomatic hematuria is indicated in males with visible condylomata. Its presence is indicative of a urethral or meatal lesion.

Management

Although the details of health care delivery for adolescents differ by state, all 50 states and the District of Columbia allow health professionals to evaluate and treat adolescents for an STI without parental consent, except in unusual circumstances. Routine laboratory screening for common STIs is recommended at least annually in all sexually active adolescents and more frequently for those with additional risk factors. Gonorrhea, chlamydia, syphilis, chancroid, and HIV/AIDS are reportable diseases in every state, and a positive laboratory result is the impetus for reporting. Notification of all sex partners within 60 days of the onset of symptoms or diagnosis of infection or, if greater than 60 days, the last sexual partner, is generally anonymous and carried out by local public health officials. Contacts are informed that a partner has been diagnosed with an STI and are instructed to be evaluated and receive appropriate treatment.

Adequate and timely treatment of all sexual partners of patients diagnosed with an STI is extremely important to prevent reinfection. Because partners often are asymptomatic and do not seek treatment, however, and because persistent and recurrent infection rates are reported to be particularly high among adolescents, expedited partner therapy (EPT) is now advocated in many states. *Expedited partner therapy* is the practice of treating the sex partners of individuals with specific STIs without an intervening formal medical evaluation or professional prevention counseling. An extension of EPT, patient-delivered partner therapy, is another practical means of providing patients with medications or prescriptions for their presumed infected partners. Care must be taken when treating the female partners of men with gonorrhea or chlamydia without an examination because of the potential for undiagnosed PID in the female partner. Per CDC guidelines, in addition to providing medications, female partners should also receive instructions about the symptoms of PID and advice on when to seek additional medical care.

Antibiotic recommendations and dosing schedules for the inpatient treatment of PID are noted in Box 60.5, as well as in Chapter 59 (Table 59.2) and Chapter 145 (Table 145.1) for other infections. The outpatient management of PID in adolescents with mild to moderate disease is supported by the 2015 CDC sexually transmitted diseases treatment guidelines; however, individual physician judgment of the teenager's ability to adhere to an outpatient regimen is crucial to prevent short- and long-term sequelae. For additional details about specific conditions and therapies, consult Selected References at the end of this chapter, specifically the CDC publication "Sexually Transmitted Diseases Treatment Guidelines, 2015." To avoid reinfection, patients and their sex partners should avoid sexual intercourse for at least 7 days after all parties have been adequately treated and symptoms have resolved.

In addition to antimicrobial therapy, treatment of the adolescent with an STI should include preventive services and counseling on risk reduction in a nonjudgmental and developmentally appropriate manner. Additionally, the patient's primary language, culture, sexual orientation, sexual practices, and age should be taken into account. Adolescents with a first-time STI and those with recurrent STIs should be educated about disease transmission, consequences of delayed treatment, and methods for the prevention of acquiring

Box 60.5. Parenteral Regimens for the Inpatient Treatment of Pelvic Inflammatory Disease

Parenteral Regimen A

Cefotetan, 2 g IV every 12 hours

or

Cefoxitin, 2 g IV every 6 hours

plus

Doxycycline,[a] 100 mg PO or IV every 12 hours

Parenteral Regimen B

Clindamycin 900 mg IV every 8 hours

plus

Gentamicin loading dose IV or IM (2 mg/kg body weight), followed by a maintenance dose of 1.5 mg/kg every 8 hours. (Single daily dosing 3–5 mg/kg may be substituted.)

The above regimens are continued for 24–48 hours after the patient improves clinically. On discharge from the hospital, doxycycline is continued orally for a total of 14 days. Clindamycin, 450 mg PO 4 times a day, can be used as an alternative to complete 14 days of treatment.

When tubo-ovarian abscess is present, clindamycin or metronidazole with doxycycline is recommended rather than doxycycline alone.

Abbreviations: IM, intramuscularly; IV, intravenously; PO, orally.

[a] Doxycycline should be administered orally when possible because of the pain associated with IV infusion.

Derived from Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. Atlanta: U.S. Department of Health and Human Services; 2015. https://www.cdc.gov/std/tg2015/clinical.htm. Accessed April 3, 2019.

new and recurrent infections (eg, abstinence, condom use, limiting the number of sexual partners, modifying sexual behaviors, asymptomatic viral shedding, pre-exposure immunization [eg, Gardasil 9, Cervarix]). The risk for acquiring other specific STIs, such as HIV, also should be addressed. The physician should spend additional time with the adolescent with recurrent STI and explore the reasons why preventive methods have failed in the past. Several factors are extremely important to consider, including an untreated or undisclosed partner, poor sexual judgment secondary to concomitant substance use or abuse, and nonadherence to previously prescribed treatment regimens.

Patient retesting in 3 months is recommended for gonorrhea, chlamydia, and trichomonas infections, even if the physician is certain the patient has been treated with an appropriate antibiotic regimen. Most posttreatment infections are the result of reinfection rather than treatment failure and occur because the sex partner did not receive treatment or from the initiation of sexual activity with a new infected partner. Because repeat infections can increase the risk for long-term complications associated with PID and because the rate of reinfection in adolescents is so high, the CDC recommends retesting all individuals in 3 months.

Prognosis

The prognosis is good in most cases in which STIs are diagnosed and managed in a timely manner, especially with the judicious use of observed single-dose oral therapy for uncomplicated chlamydial infection, which is the most common bacterial STI in adolescents. Acute complications of PID include TOA and Fitz-Hugh–Curtis syndrome, which can result in an unanticipated surgical procedure or prolonged hospitalization. Long-term consequences of PID are chronic abdominal or pelvic pain, ectopic pregnancy, and tubal infertility. Early administration of appropriate antibiotics and prevention of recurrent infection is crucial to minimize the manifestation of these long-term sequelae.

Currently, no pharmacologic agent exists for eradicating HSV-1 and HSV-2, although acyclovir, famciclovir, and valacyclovir are useful in managing the signs and symptoms of primary herpes and reducing the incidence and duration of recurrences. The long-term safety of HSV treatment with valacyclovir or famciclovir for longer than 1 year is unknown. Daily suppressive therapy to reduce the frequency of outbreaks may be warranted in patients with more than 6 outbreaks per year. Because recurrences often decrease over time, the need for suppressive therapy should be assessed annually.

The prognosis for HIV is variable, depending on the individual's disease progression at the time of diagnosis and adherence to antiretroviral therapy. The advent of new preventive therapies, such as HIV pre-exposure prophylaxis, has significantly reduced the risk of HIV infection in individuals at substantial risk (eg, those exposed to HIV through sex or injection drug use). When taken daily and consistently, a combination of emtricitabine and tenofovir (eg, Truvada, Descovy) can reduce the risk of permanent infection by up to 92%. These medications should be used in combination with other medications to manage established HIV infection as well.

CASE RESOLUTION

A diagnosis of HSV-1 and HSV-2 infection can be made clinically. The diagnosis can be confirmed by unroofing a vesicle and gently swabbing the ulcer to examine for HSV via PCR testing. The adolescent should be counseled about HSV and its general mode of transmission, the natural history of primary versus recurrent infection, and the role of antiviral agents. A urine sample also should be sent for NAAT for the detection of gonorrhea and chlamydia. A serum RPR or VDRL test should be performed as well as a thorough assessment for HIV risk. Testing for HIV should be strongly encouraged, allowing the patient time to ask questions or decline testing. The adolescent should be given a return appointment for 1 to 2 weeks hence to review laboratory results, discuss possible treatment options for recurrent HSV-1 and HSV-2 infection, and explore risk-reduction behavior. Depending on the results of the remainder of the STI screening tests, the adolescent should be followed every 3 to 6 months.

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CHAPTER 61

Menstrual Disorders

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CASE STUDY

A 16-year-old girl presents with a 9-day history of vaginal bleeding. She has no history of abdominal pain, nausea, vomiting, fever, dysuria, or anorexia, and she reports no dizziness or syncope. Her menses usually lasts 4 to 5 days and, in general, occurs monthly. Her last menstrual period was 3 weeks ago and was normal in duration and flow. Menarche occurred at 14 years of age. She is sexually active, has had 2 partners, and reportedly uses a condom "most of the time." Neither she nor her current partner has ever been diagnosed with or treated for a sexually transmitted infection. She has no family history of blood dyscrasia or cancer, has no history of chronic illness, and takes no medications.

On physical examination, she is in no acute distress. Her temperature is 36.9°C (98.4°F). Her heart rate is 100 beats/min, and her blood pressure is 110/60 mm Hg. Her body mass index is at the 50th percentile. The physical examination, including a pelvic examination, is unremarkable except for minimal blood noted at the vaginal introitus.

Questions

1. What menstrual disorders commonly affect adolescent girls?
2. What factors contribute to the manifestation of menstrual disorders, particularly during adolescence?
3. What relevant menstrual history should be obtained from the adolescent?
4. What options are available for managing primary dysmenorrhea?
5. How is abnormal uterine bleeding managed in the adolescent patient?

Gynecologic concerns and symptoms are common reasons for adolescent girls to visit their primary care physician. The challenge for the pediatrician is to differentiate between an organic etiology, a functional condition, and psychogenic symptoms. When this cannot be readily done or if the physical examination is equivocal, multiple diagnostic procedures may be performed, often with variable results. Additionally, many pediatricians are uncomfortable evaluating gynecologic problems in adolescents and performing pelvic examinations, which contributes to this diagnostic dilemma. The purpose of this chapter is to review some of the more common gynecologic conditions affecting adolescent girls and to highlight the significant historical and physical findings associated with each problem. For a discussion of the infectious conditions that cause pelvic pain, see Chapter 60.

Epidemiology

The overall prevalence of menstrual disorders during adolescence is estimated to be 50% in the United States, with the most common gynecologic symptom being *dysmenorrhea*, or painful menstruation. At least 70% to 90% of women have some pain associated with menses; the extent of discomfort varies. Although most menstruating women report mild to moderate discomfort, severe dysmenorrhea occurs in 10% to 15% of women and has been reported to be responsible for significantly limiting activities of daily living, including school attendance, participation in athletics, and socialization with peers. Uterine anomalies or pelvic abnormalities (eg, endometriosis) occur in approximately 10% of female adolescents and young women with severe dysmenorrhea.

Prevalence estimates concerning premenstrual syndrome (PMS) are difficult to assess because most studies in adolescents are retrospective, and self-reports can be unreliable and misleading. In these studies, between 20% and 30% of older adolescents report significant PMS-type symptoms. An estimated 20% to 40% of adult women experience PMS symptoms sufficiently bothersome to impair daily functions, and 5% to 10% have debilitating symptoms that warrant the diagnosis of premenstrual dysphoric disorder (PMDD). Other menstrual problems in adolescents include abnormal uterine bleeding, primary and secondary amenorrhea, and vaginal discharge.

Several factors contribute to the occurrence of menstrual disorders in adolescence. The average age of menarche in the United States remains at 12.5 years (range: 9–16 years), although the age of onset of puberty has decreased in some racial groups and in children with obesity. Bleeding may be irregular or prolonged initially in young adolescents because most early menstrual cycles are anovulatory and irregular, especially during the first few years after menarche. Bleeding problems may resolve after ovulatory cycles are established; however, menstrual symptoms, such as lower abdominal pain, breast tenderness, headache, bloating, and vomiting, may predominate. Early sexual activity among adolescents and associated sexually transmitted infections (STIs) also may contribute to the presence of certain gynecologic conditions in this age group, particularly vaginitis, abnormal uterine bleeding, and pelvic pain.

Clinical Presentation

The adolescent with a menstrual disorder may present in a variety of ways. Specific symptoms include heavy menstrual bleeding, irregular periods, and painful menses, and more general symptoms include fatigue, dizziness, and syncope (Box 61.1). The adolescent with PMS may experience mood swings, stress, and nervousness accompanied by abdominal bloating and pain before menses. Additionally, the adolescent or her parent or guardian may have questions or concerns about delayed pubertal development and primary or secondary amenorrhea.

Pathophysiology

Puberty and the Normal Menstrual Cycle

Figure 61.1 depicts the menstrual cycle, which typically lasts for 21 to 35 days, with a mean length of approximately 28 days. Normal duration of menses is 4 to 7 days. Blood loss is usually 30 to 40 mL per cycle; most women do not lose more than 60 mL per cycle. Regular ovulatory cycles usually do not occur until 2 to 3 years after menarche, although 10% to 20% of cycles remain anovulatory as long as 5 years after menarche. It has been reported that girls with earlier menarche establish regular ovulatory menstrual cycles more rapidly than girls with later menarche.

One-quarter of females begin menstruating when they reach sexual maturity rating (SMR [ie, Tanner stage]) 3 of sexual maturation, but approximately two-thirds do not menstruate until they reach SMR 4 breast and genital development. Several other processes occur before the onset of menstruation. *Thelarche*, or the beginning of breast development, takes place approximately 2 to 3 years before menarche, and growth acceleration usually begins approximately 1 year before thelarche.

Dysmenorrhea

Dysmenorrhea often is accompanied by other symptoms, such as nausea, vomiting, diarrhea, fatigue, bloating, low back pain, and headaches. It can be classified as primary or secondary. Primary dysmenorrhea occurs in the absence of any pelvic pathology,

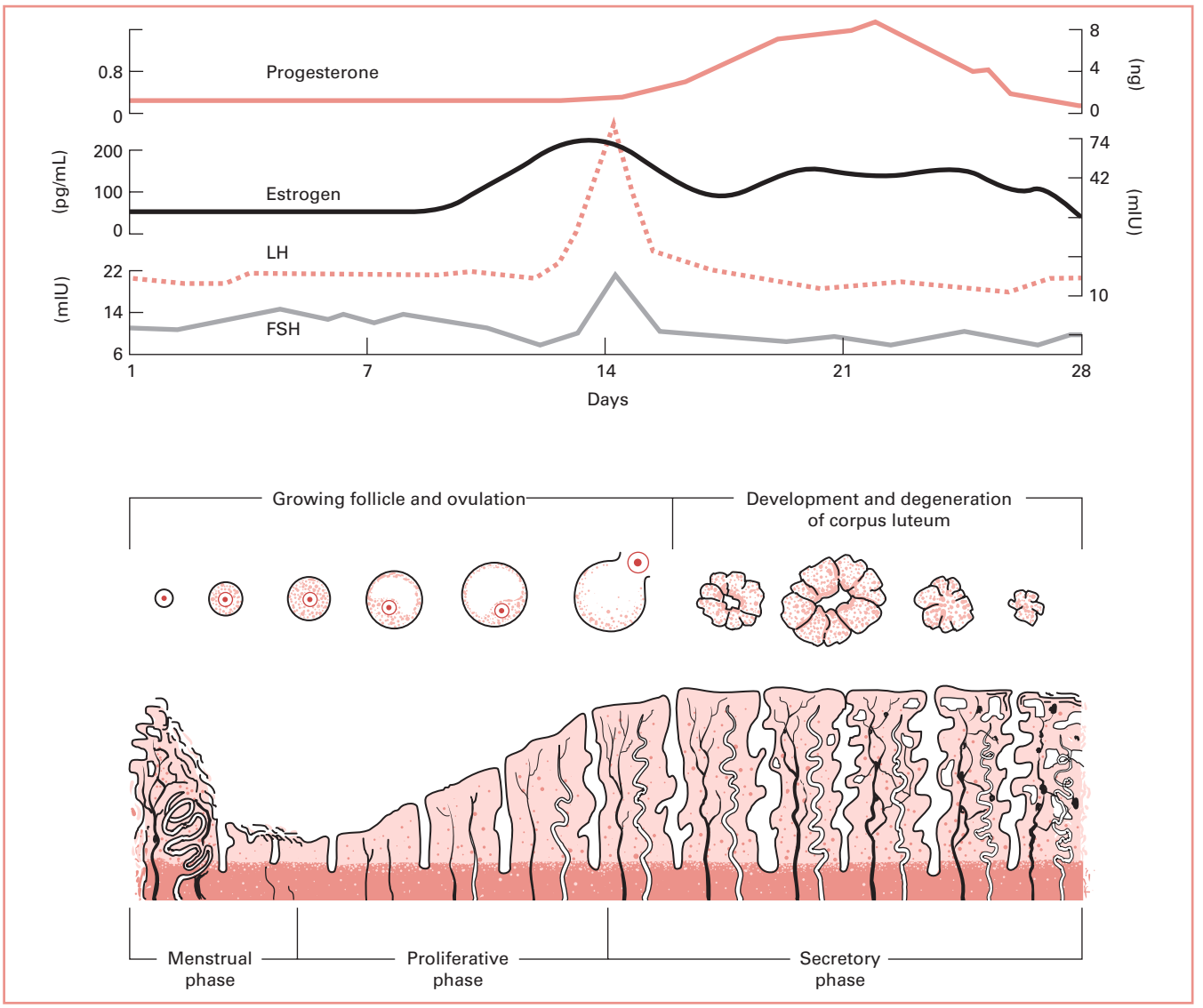

Figure 61.1. The normal ovulatory menstrual cycle.
Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Box 61.1. Diagnosis of Menstrual Disorder in the Adolescent Patient

Primary Dysmenorrhea

- Painful menstruation
- Lower abdominal pain associated with menstruation, usually worse on the first few days of bleeding
- Associated back pain
- Pain sometimes accompanied by nausea, vomiting, fatigue, headache, bloating, and diarrhea
- Symptoms begin 6–12 months after menarche

Abnormal Uterine Bleeding

- Prolonged bleeding (>8 days) *or*
- Excessive bleeding (>6 tampons/pads per day) *or*
- Frequent uterine bleeding (≤21 days)
- No demonstrable organic etiology
- Normal laboratory studies, with the possible exception of anemia

Primary Amenorrhea

- No spontaneous menstruation in a girl of reproductive age
- Absence of menarche by age 15 years in a girl with normal pubertal development *or*
- Absence of menarche by age 13 years in a girl with no secondary sexual development *or*
- Absence of menarche within 1–2 years of reaching full sexual maturation (sexual maturity rating 5)

comprising 90% of adolescent menstrual pain, and most commonly occurs in older adolescents after ovulatory cycles are established. *Secondary dysmenorrhea* refers to painful menses associated with some underlying pelvic pathology, such as pelvic inflammatory disease (PID), endometriosis, ovarian cysts or tumors, Müllerian anomalies, or cervical stenosis. A complete list of causes of secondary amenorrhea can be found in Box 61.2. Endometriosis is the most common cause of secondary dysmenorrhea in the adolescent.

Numerous studies have shown that cell membrane phospholipids, endometrial prostaglandins, and leukotrienes play a role in the pathogenesis of primary dysmenorrhea. After ovulation, fatty acids build up in the phospholipids of the cell membrane in response to the production of progesterone. Arachidonic acid as well as other omega-6 fatty acids are released after the onset of progesterone withdrawal before menstruation. A cascade of prostaglandins and leukotrienes is initiated in the uterus during menses, which results in an inflammatory response. Prostaglandin $F_{2\alpha}$, which is produced locally by the endometrium from arachidonic acid, is a potent vasoconstrictor and myometrial stimulant that causes uterine contractions, resulting in tissue ischemia and pain. Prostaglandin $E_{2\alpha}$ causes hypersensitivity of the pain nerve terminals in the uterine myometrium. The cumulative effect of these prostaglandins may cause the pain of primary dysmenorrhea. Hormonal and endocrine factors also may play a role in the etiology of primary dysmenorrhea, because ovulatory cycles with estrogen and progesterone are necessary for development of the condition.

Box 61.2. Differential Diagnosis of Common Menstrual Disorders

Secondary Dysmenorrhea

- Endometriosis
- PID
- Uterine myomas, polyps, or adhesions
- Adenomyosis
- Ovarian cysts or tumors
- Presence of an intrauterine device
- Cervical stenosis or strictures
- Congenital malformations (ie, septate uterus, imperforate hymen)

Excessive Uterine Bleeding

- Ovulatory dysfunction: physiologic anovulation
- Complications of pregnancy: spontaneous/threatened/incomplete abortion, ectopic pregnancy, hydatidiform mole
- Infections of the lower and upper genital tract: endometritis, PID, cervicitis/vaginitis
- Blood dyscrasia and thrombocytopenia: von Willebrand disease, ITP, leukemia, platelet defects, aplastic anemia
- Endocrine disorders: hypothyroidism and hyperthyroidism, hyperprolactinemia, late-onset 21-hydroxylase deficiency, Cushing or Addison disease, PCOS
- Vaginal anomaly: carcinoma
- Cervical/uterine abnormalities: endometriosis, polyp, hemangioma, rhabdomyosarcoma
- Ovarian abnormalities: primary ovarian failure, tumors, cysts
- Systemic/chronic illness: IBD, malignancy, SLE, diabetes mellitus
- Foreign body: retained condom or tampon, IUD
- Medications: aspirin, anticoagulants, hormonal contraception, androgens, chemotherapy
- Trauma or sexual assault (ie, high vaginal laceration)

Amenorrhea (Primary and Secondary)

- Pregnancy
- Systemic abnormalities: endocrinopathies (hypothyroidism, Cushing syndrome), chronic diseases (IBD, sickle cell disease), poor nutrition (anorexia nervosa), obesity, intense exercise, stress, drugs (opiates, valproate)
- Hypothalamic lesions: tumors, infiltrative lesions (TB, CNS leukemia)
- Pituitary lesions: prolactinoma, drugs causing elevated prolactin (eg, marijuana, cocaine), cranial irradiation
- Ovarian failure: gonadal dysgenesis (ie, Turner syndrome); autoimmune failure associated with diabetes mellitus, adrenal insufficiency, thyroid disease, and celiac disease; radiation- or chemotherapy-induced oophoritis; galactosemia
- Congenital abnormalities of the reproductive tract: imperforate hymen, transverse vaginal septum, absence or abnormality of the uterus, complete androgen insensitivity syndrome (complete or partial receptor defects), Mayer-Rokitansky-Küster-Hauser syndrome
- Androgen excess: PCOS, benign ovarian androgen excess

Abbreviations: CNS, central nervous system; IBD, inflammatory bowel disease; ITP, idiopathic thrombocytopenic purpura; IUD, intrauterine device; PCOS, polycystic ovary syndrome; PID, pelvic inflammatory disease; SLE, systemic lupus erythematosus; TB, tuberculosis.

Most cases of primary dysmenorrhea begin 1 to 2 years after menarche, and symptoms gradually increase until patients reach their early 20s. Parity and advancing age are associated with a decrease in symptomatology.

Abnormal Uterine Bleeding

Abnormal uterine bleeding (formerly called dysfunctional uterine bleeding) is abnormal or excessive endometrial bleeding in the absence of any pelvic pathology. Menstruation is considered excessive if the cycles are short (≤21 days) and the bleeding is prolonged (>8 days). Although ovulatory dysfunction is the most common cause of abnormal or excessive uterine bleeding in adolescents, it is a diagnosis of exclusion. Other causes of abnormal bleeding should first be investigated by obtaining a thorough history, performing a complete physical examination, and obtaining laboratory studies as indicated.

Excessive uterine bleeding typically is the result of anovulatory, immature menstrual cycles. In adolescents, 50% of menstrual cycles are anovulatory within the first 2 years after menarche. If menarche occurs later in adolescence (ie, at SMR 5), the interval from anovulatory to ovulatory cycles reportedly lasts even longer. Most cases of abnormal uterine bleeding in adolescents are thought to result from the delayed maturation of the hypothalamic-pituitary-ovarian axis. Normally, a positive feedback mechanism manifests with rising estrogen levels, resulting in a surge in luteinizing hormone and follicle-stimulating hormone, which triggers ovulation. The progesterone-producing corpus luteum then stimulates development of the secretory endometrium, with subsequent shedding after approximately 14 days if no fertilization occurs (ie, menses). With anovulation, progesterone-producing corpus luteum is absent; thus, no development of a secretory endometrium occurs. Estrogen thus remains unopposed, and proliferative endometrium continues to accumulate. When the tissue can no longer maintain its integrity, it sloughs. Additionally, without progesterone the normal vasospasm that helps limit endometrial bleeding does not occur. As a result, bleeding is prolonged, frequent, and heavy.

Premenstrual Syndrome

Premenstrual syndrome refers to a group of physical, cognitive, affective, and behavioral symptoms that occur 1 to 2 weeks before menses, that is, during the luteal phase of the menstrual cycle, and resolve within 4 days after the onset of menstruation. Various mechanisms have been proposed, including an increased sensitivity to the normal cyclic fluctuations in steroid hormones and releasing factors and alterations in central neurotransmitters, such as endorphins, γ-aminobutyric acid, and serotonin. The exact etiology remains unknown, however, despite multiple studies with a focus on pinpointing the cause of this complex condition.

Amenorrhea

Amenorrhea is the lack of spontaneous menstruation in women of reproductive age. Similar to dysmenorrhea, it can be classified as primary or secondary. Traditionally, primary amenorrhea was defined by the following criteria: an absence of menarche by age 16 years in the girl with otherwise normal pubertal development, an absence of menarche by age 14 years in the girl with no secondary sexual development, and an absence of menarche within 1 to 2 years of reaching SMR 5 pubic hair. Causes of primary amenorrhea range from congenital anatomic anomalies to genetic and endocrine conditions. Because many of these disorders can be diagnosed and treated earlier than 16 years of age, however, guidelines have been modified to address when menstrual conditions should be evaluated. Current guidelines encourage a more proactive medical evaluation for girls who lack menses by age 15 years or more than 3 years after the onset of secondary sexual development. Additionally, absence of secondary sexual characteristics by age 13 years is considered abnormal (Box 61.3). A detailed discussion of each etiology that causes primary amenorrhea is beyond the scope of this chapter; see Selected References for more information.

Secondary amenorrhea is a state of 3 or more consecutive months of amenorrhea in the girl who has already established menstruation. The most common cause of secondary amenorrhea is pregnancy, which must be ruled out in all adolescents presenting with this symptom, regardless of their acknowledgment of sexual activity. Other causes include systemic illness, significant change in weight, stress, intense physical exertion, eating disorders (eg, anorexia nervosa), and certain medications, such as phenothiazines, glucocorticoids, and heroin. Polycystic ovary syndrome is another common cause of secondary amenorrhea in young adult women, but often it is characterized by a wide range of menstrual irregularities, including abnormal uterine bleeding, oligomenorrhea, and amenorrhea of perimenarcheal onset.

Box 61.3. Menstrual Conditions That May Require Evaluation

Menses That:

- Have not started within 3 years of thelarche
- Have not started by 13 years of age with no signs of pubertal development
- Have not started by 14 years of age with
  - Signs of hirsutism *or*
  - A history or physical examination suggestive of excessive exercise or eating disorder *or*
  - Concerns about an outflow tract obstruction or anomaly
- Have not started by 15 years of age
- Are regular, occurring monthly, then become markedly irregular
- Occur more frequently than every 21 days or less frequently than every 45 days
- Occur 90 days apart even for 1 cycle
- Last longer than 7 days
- Require frequent pad/tampon changes (soaking more than 1 every 1–2 hours)

Adapted with permission from American College of Obstetricians and Gynecologists Committee on Adolescent Health Care. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Committee Opinion No. 651. *Obstet Gynecol*. 2015;126:e143-6.

Vaginal Discharge

Vaginal discharge can be normal (ie, physiologic), nonspecific, or related to a particular bacterial or viral pathogen. A thin, white discharge, known as *leukorrhea*, occurs approximately 6 to 12 months before the onset of menarche. A purulent, malodorous, or bloody discharge is considered abnormal, however. Etiologies are varied and may be infectious, inflammatory, or traumatic (see Chapters 59 and 60).

Differential Diagnosis

The differential diagnosis of common menstrual disorders is extensive and can be found in Box 61.2. Other etiologies of pelvic pain include mid-cycle menstrual disorders (eg, mittelschmerz), urinary tract infection, complications of unmanaged or inadequately managed PID, and abdominal conditions, such as inflammatory bowel disease and irritable bowel syndrome. Psychogenic pain also should be considered as a cause of recurrent pelvic pain and may be secondary to depression, anxiety, a history of sexual abuse, or another psychological condition.

Evaluation

History

A thorough medical and family history should be obtained from the adolescent girl with a suspected menstrual disorder because many nongynecologic conditions can affect menses. A complete psychosocial assessment, including a private, confidential sexual history, also should be performed without the parent or guardian present. The acronym HEADSS (home, employment and education, activities, drugs, sexuality, suicide/depression) serves as a useful tool when interviewing adolescents (see Chapter 4).

Most of the interview should focus on the gynecologic history (Box 61.4), including pattern of menstrual bleeding and any associated symptoms (Box 61.5). With primary dysmenorrhea, pain that

Box 61.4. Gynecologic History

- Age at menarche
- Date of last menstrual period
- Regularity of menses
- Duration and pattern of bleeding
- Amount of flow (ie, number of pads and/or tampons used per day and amount of saturation)
- Associated menstrual symptoms, such as bloating, headache, lower abdominal pain, and cramping
- Maternal and sibling gynecologic history
- Treatment of menstrual symptoms
- Sexual activity (consensual and nonconsensual)
- Age at debut
- Number of partners and ages
- Date of last sexual encounter
- Protected versus unprotected vaginal or anal intercourse
- Current method of contraception

Box 61.5. What to Ask

Menstrual Disorders

Dysmenorrhea

- What is the pain like?
- Does it always occur with menses?
- When did the pain first begin in relation to menarche?
- How frequently does the pain occur?
- How long does the pain last?
- Are any other symptoms associated with the pain (eg, nausea, vomiting, diarrhea, headache)?
- Do you miss a lot of school or work as a result of painful menses?
- Do the painful menses interfere with other activities?
- What do you do for the pain? Have you tried any medications or complementary or alternative remedies?
- Does a maternal or sibling history exist of painful menses?
- Does a family history exist of endometriosis?

Abnormal Uterine Bleeding

- What was the age at menarche?
- Do you have any symptoms of anemia (eg, fatigue, dizziness, shortness of breath)?
- Have you experienced any syncopal episodes?
- Do you have any history of blood loss in the urine or stool?
- Do you have any evidence of a bleeding disorder (eg, easy bruising, bleeding from the gums or nares)?
- Do you have any symptoms of pregnancy (eg, breast tenderness, morning nausea or vomiting, fatigue)?
- Have you knowingly been exposed to a sexually transmitted infection?
- Has your weight or diet changed markedly?
- Are you using any medications, such as aspirin, oral contraceptives, long-acting progestational agents, psychotropic medications, or anticoagulants?
- Do you have a history of a systemic illness, such as systemic lupus erythematosus, diabetes mellitus, or renal disease? Do you have a history of trauma?
- Is the bleeding cyclic in nature?
- Does breakthrough bleeding occur throughout the cycle?
- Does a family history exist of bleeding disorders, type 2 diabetes mellitus, polycystic ovary syndrome, or thyroid disease?

Amenorrhea

- Have you ever had a period?
- Have you noticed any other changes associated with puberty (eg, breast development, pubic hair, growth spurt)?
- Do you have any other symptoms, such as galactorrhea, weight loss, or hirsutism?
- Have you experienced significant changes or stressors in your life (eg, parental divorce, new school)?
- How often do you exercise?
- What is your typical diet, or do you have any dietary restrictions (eg, vegan, vegetarian)?
- Are you taking any medications, including contraception?
- Do you have a history of headaches or visual changes?
- Does the review of systems reveal anything suggestive of a chronic illness, such as Crohn disease?

radiates to the anterior thighs or the lower back is not uncommon, although other emergent etiologies, such as ovarian torsion, must be explored if the patient presents acutely. The color of the blood may be helpful when assessing excessive uterine bleeding. Brown or dark blood may be associated with a cervical obstruction or endometriosis, whereas red or pink blood occurs with most other conditions. More important, the timing of the bleeding is extremely significant. Cyclic bleeding beginning at menarche is more consistent with the presence of a blood dyscrasia. In contrast, breakthrough bleeding throughout the cycle may be indicative of an infection, endometriosis, or a polyp. The passage of blood clots on rising in the morning is not uncommon secondary to the vaginal pooling of blood while the patient is supine. Clots throughout the day, however, are not normal and require further investigation.

A thorough review of systems also should be performed, paying particular attention to recent weight changes, systemic illnesses, and chronic symptoms.

Physical Examination

A complete physical examination, including an evaluation for any stigmata associated with a systemic illness, must be performed in the adolescent girl with a suspected menstrual disorder. The patient's height and weight should be plotted on the growth chart and compared with previous measurements. Depending on the SMR, the health professional can then determine if the teenager should have experienced her expected growth spurt. Body mass index, calculated by dividing weight in kilograms by height in meters squared, also should be calculated and compared with previous values, especially in girls with amenorrhea. Vital signs, including orthostatic measurements, are especially important to review in the patient with excessive uterine bleeding or amenorrhea as the result of restrictive eating (eg, hypothermia, severe bradycardia, orthostatic hypotension). The skin should be inspected for any evidence of androgen excess (eg, hirsutism, acne), insulin resistance (acanthosis nigricans), bruising, pallor, or petechiae. The thyroid gland should be palpated for masses or any evidence of hypertrophy, and the abdomen and suprapubic area also should be palpated for tenderness, organomegaly, or masses.

In the presence of a chaperone, the SMR of the breasts should be noted and compared with pubic hair development, particularly in the adolescent with primary amenorrhea. Other signs compatible with gonadal dysgenesis include webbed neck, broad shield-like chest, short fourth metacarpal, and an increased carrying angle of the arms. The presence or absence of galactorrhea also should be noted by gently squeezing each nipple. With the patient in the lithotomy or frog-leg position, the external genitalia should be carefully inspected for clitoral size (normal clitoral glans width, 2–4 mm) and patency of the hymen via gentle separation/traction of the labia majora. Passing a saline-moistened cotton swab gently through the vaginal introitus can help determine vaginal length as well as the presence of a transverse or longitudinal vaginal septum. A bimanual vaginal or rectoabdominal examination may be performed in the adolescent with primary amenorrhea who is not sexually active to ensure the presence of a normal vagina, uterus, and adnexa. Typically, a speculum examination is not necessary for an adolescent with no prior sexual intercourse who is reporting abnormal uterine bleeding or simple primary dysmenorrhea. If the sexually active teenager is asymptomatic, screening tests for STIs, particularly chlamydia and gonorrhea, can be performed noninvasively using a voided urine sample or self-collected vaginal swab, and the pelvic examination can be deferred. In the adolescent who is sexually active and has abnormal vaginal discharge, intermenstrual bleeding, history of dyspareunia, or lower abdominal pain, however, a complete pelvic and bimanual examination is mandatory to evaluate for PID and its complications (eg, tubo-ovarian abscess).

Laboratory Tests

The performance of laboratory studies depends on the specific menstrual symptoms. No laboratory studies initially are necessary for primary dysmenorrhea because the diagnosis usually is based on a classic clinical history and normal physical examination. The same is true for PMS. The laboratory evaluation for primary amenorrhea is dependent on the presence or absence of associated secondary sexual characteristics. For more information on the diagnostic evaluation of primary and secondary amenorrhea, refer to Selected References.

In the patient with abnormal uterine bleeding, baseline studies must include obtaining hemoglobin or hematocrit. Other initial laboratory studies should include a complete blood cell count to evaluate the red cell indices and platelets, a reticulocyte count, and a urine pregnancy test. Further diagnostic studies depend on the severity of the anemia and findings on history and physical examination. These may include coagulation studies (eg, prothrombin time/partial thromboplastin time), erythrocyte sedimentation rate, and thyroid function tests. Other tests for the evaluation of a blood dyscrasia, such as a von Willebrand factor (measured with ristocetin cofactor activity and antigen), factor VIII, and fibrinogen, should be performed in the patient who presents with severe anemia, especially at menarche or shortly thereafter. The studies should be performed in consultation with a pediatric hematologist and obtained before the administration of any required blood transfusions or hormonal treatment (eg, estrogen-containing medications), which may affect the results of certain assays. If the patient is sexually active and a pelvic examination is performed, an endocervical specimen should be obtained for nucleic acid amplification testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae.* Nucleic acid amplification testing of the urine or a vaginal swab to screen for gonorrhea and chlamydia are also available (eg, ligase chain reaction, polymerase chain reaction). Follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone, testosterone, free and total testosterone, and dehydroepiandrosterone sulfate studies should be performed in the patient with a history of chronic anovulation or in whom androgen excess is suspected (eg, polycystic ovary syndrome).

Imaging Studies

Transabdominal or transvaginal pelvic ultrasonography can be helpful in the patient with excessive uterine bleeding or amenorrhea if a mass is suspected or palpated on physical examination. Complex

congenital obstructive anomalies, such as a longitudinal vaginal septum with hemi-obstruction, cervical agenesis or stenosis, or a partially obstructing uterine septum, may require magnetic resonance imaging if pelvic ultrasonography is inconclusive. Plain radiography is not indicated. Magnetic resonance imaging of the head may be indicated in the adolescent with amenorrhea if the patient presents with central nervous system symptoms or has markedly elevated serum prolactin.

Management

Effective management of each of these adolescent gynecologic conditions is multifaceted and includes education of the patient and parent or guardian, reassurance about the ease of managing the condition, and appropriate medications for those conditions requiring therapy. Generally, for most gynecologic conditions a menstrual calendar can be quite helpful for confirmation of the severity of the bleeding and assessment of the pattern and duration of each menstrual cycle. Digital period tracking applications are available for download onto most smartphones to assist with monthly documentation of menses and associated symptoms.

Dysmenorrhea

General modalities in the management of primary dysmenorrhea include education about menstruation, proper nutrition, smoking cessation (as appropriate), application of heat (eg, heating pad), simple exercise and/or yoga, acupuncture, and pharmacologic therapies.

For mild to moderate symptoms of dysmenorrhea, over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are appropriate for first-line pain management and can also reduce blood loss. Physicians most often suggest that patients use ibuprofen initially because it is both safe and efficacious when taken in appropriate doses and frequency. The dose is 400 to 600 mg every 6 to 8 hours. Ibuprofen should be taken at the onset of the menstrual cycle and continued for 24 to 72 hours or for the usual duration of symptoms. Any girl who is unable to take the medication at the onset of menses secondary to vomiting can be instructed to start the NSAID 1 to 2 days before menses is expected to occur.

For moderate to severe dysmenorrhea in the patient who is not sexually active and does not desire birth control, a faster-acting NSAID, such as naproxen, may be an alternative to ibuprofen (Table 61.1). The major mechanism of action of NSAIDs is the inhibition of prostaglandin synthesis. A loading dose of naproxen is recommended at the onset of therapy. Side effects of these drugs, which most commonly affect the gastrointestinal tract, are nausea, vomiting, and dyspepsia. These reactions can be minimized by taking the medication with food or an antacid. Other adverse reactions include renal effects; skin reactions, such as erythema multiforme and urticaria; and central nervous system effects, including headache and dizziness. Contraindications to NSAID use include peptic ulcer disease, clotting disorders, and renal disease. All NSAIDs should be administered with food and taken for 3 to 4 menstrual cycles before their efficacy is evaluated.

Table 61.1. Nonsteroidal Anti-inflammatory Drugs Used in the Management of Primary Dysmenorrhea

Generic	*Sample Trade Name(s)*	*Dosage*
Ibuprofen	Motrin, Advil (200 mg/tablet)	2–3 tablets every 6–8 hours for 24–72 hours
Naproxen sodium	Aleve (220 mg/tablet), Anaprox (275 mg/tablet), Naprosyn (250 mg/tablet)	2 tablets at onset, then 1 tablet every 8–12 hours
Mefenamic acid	Ponstel (250 mg/capsule)	2 capsules at onset, then 1 capsule every 6 hours or 2 capsules every 8 hours

Low-dose combination oral contraceptive is indicated for the adolescent with moderate or severe dysmenorrhea who is sexually active or in the patient whose symptoms are not sufficiently relieved by NSAIDs alone and whose own medical or family history does not preclude the use of estrogen. Oral contraceptives decrease the production and release of prostaglandins and leukotrienes by inhibiting ovulation as well as endometrial growth. Because the symptoms of dysmenorrhea are prevented only after several cycles of oral contraceptive pill (OCP) use, the patient should be advised not to expect complete resolution of symptoms during the first month of treatment. The adolescent with a classic clinical presentation of primary dysmenorrhea does not require a pelvic examination before initiating oral contraceptives. Even if an adolescent is sexually active, routine STI screening can be performed using a vaginal swab or urine-based nucleic acid amplification testing. Reevaluation after at least 3 cycles is indicated to document adherence and resolution or improvement of menstrual symptoms.

Thirty or 35 mcg of ethinyl estradiol-containing monophasic oral contraceptives should be used for a minimum of 3 to 4 months. If symptoms do not improve, an NSAID can be added to the treatment regimen. Oral contraceptives are more than 90% effective in cases of severe dysmenorrhea, and the physician should emphasize this hormonal benefit to the patient and the patient's parent or guardian. Although 20 mcg of ethinyl estradiol-containing OCP formulations are available, the literature remains inconclusive concerning the first-line use of these for primary dysmenorrhea.

Other combined hormonal contraceptives, such as the transdermal patch and the contraceptive ring, have been studied for the management of primary dysmenorrhea in adult women. The use of extended OCP regimens to reduce the hormone-free interval also has been reported to be beneficial in reducing painful menses. Specific studies in adolescents, however, are extremely limited. Long-acting reversible contraception also should be considered in the adolescent with primary dysmenorrhea who is unable to take combined oral contraceptives.

If dysmenorrhea persists despite the judicious use of NSAIDs and contraceptives, a search for other pelvic pathology (eg,

endometriosis) is warranted, and the patient should be referred to a gynecologist for further evaluation and possible diagnostic laparoscopy.

Abnormal Uterine Bleeding

The management of abnormal uterine bleeding depends on the severity and frequency of the bleeding, the severity of anemia, and the underlying etiology (Table 61.2). The goal of management is 4-fold: to control the bleeding, correct the anemia, replenish iron stores, and prevent further episodes of bleeding. The patient with mild or moderate anemia can be treated as an outpatient with weekly to monthly follow-up depending on how quickly the bleeding is controlled and the anemia resolves. Regardless of the etiology, hormone treatment generally is required to stabilize the endometrium and control future bleeding episodes, particularly if the patient presents with symptomatic anemia. Monophasic combined oral contraceptive pills (COCPs) are the mainstay of treatment for abnormal uterine bleeding in the patient with moderate anemia and/or who desires birth control. Other hormone regimens, such as progestin-only preparations (eg, medroxyprogesterone acetate), also can be used. This is especially important in the adolescent with a medical contraindication to estrogen or disinterest in COCP therapy. Supplemental oral iron therapy is also required for all teenage girls with anemia. Prescribing ferrous gluconate rather than ferrous sulfate may improve adherence because the former is less irritating to the stomach.

Most adolescent girls with severe bleeding and symptomatic anemia require a more extensive evaluation, and such patients usually are hospitalized for appropriate parenteral intravenous fluid therapy and possible blood transfusion. Occasionally, intravenous conjugated estrogens are required every 4 to 6 hours for the first 24 hours to stop severe acute hemorrhage. Most adolescents only require 1 or 2 doses. Intravenous estrogens should not be used in the patient with a contraindication to estrogen (eg, deep vein thrombosis) or who is not currently bleeding heavily. Otherwise, in cases of moderate to severe anemia, a COCP containing 30 or 35 mcg ethinyl estradiol is initiated 3 to 4 times a day; the progesterone component is necessary to stabilize the endometrium. Additionally, an antiemetic agent often is required 1 hour before the OCP during the first few days of therapy. After bleeding is controlled, the frequency of OCP administration can be tapered, and the adolescent can continue a monophasic COCP daily, skipping the placebo pills for at least the first cycle, and then switching to a lower-dose combination oral contraceptive for at least 6 cycles total. Studies have demonstrated that 20% to 25% of adolescents who require hospitalization for severe anemia within the first year after menarche have an underlying coagulopathy and therefore warrant a thorough hematologic investigation. In the case of excessive uterine bleeding in which oral contraceptives are used but the patient does not desire birth control, hormonal therapy should not be stopped until at least 3 months after the anemia has resolved to ensure restoration of iron stores.

Surgical treatment, such as dilatation and curettage, is rarely indicated in the adolescent patient and is reserved for individuals refractory to aggressive medical treatment.

Premenstrual Syndrome

The early identification of PMS or PMDD in the adolescent can be facilitated using screening questionnaires such as The Premenstrual Symptoms Screening Tool for Adolescents, a validated tool revised for use in teenagers that scores the severity of premenstrual symptoms

Table 61.2. General Guidelines for the Management of Abnormal Uterine Bleeding in the Adolescent

Factor	*Mild Anemia*[a]	*Moderate Anemia*[b]	*Severe Anemia*[c]
Hemoglobin (g/dL)	>11	8–11	≤7
Management	Reassurance, menstrual calendar, supplemental iron twice daily, COCP 1 pill daily (the latter if sexually active). Consider NSAID to help reduce blood loss.	Initially, 3–4 monophasic COCPs (30–35 mcg ethinyl estradiol and potent progestational agent[d]) every 6–8 hours for 2–3 days or until bleeding stops; take with antiemetic; taper to every 12 hours for 2–3 days, then every day after bleeding has stopped; skip placebos in first pill pack; then cycle for minimum of 3–6 months; prescribe oral iron supplementation. Consider NSAID to help reduce blood loss. Menstrual calendar.	Hospitalization if signs of hypovolemia or severe anemia; consider IV estrogen until bleeding stops; begin 3–4 monophasic COCPs (30–35 mcg ethinyl estradiol and potent progestational agent[d]) every day with antiemetic and taper as with moderate anemia over next 21 days; skip placebo pills for at least 1 month or until hemoglobin has normalized; then cycle with monophasic COCPs (30–35 mcg ethinyl estradiol) for 6–12 months; prescribe oral iron supplementation. Menstrual calendar.
Follow-up	2–3 months; repeat hemoglobin.	2–3 weeks for repeat hemoglobin, then every 2–3 months.	1–2 weeks for repeat hemoglobin, then every month.

Abbreviations: COCP, combination oral contraceptive pill; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

[a] Blood pressure and heart rate stable.

[b] Blood pressure and heart rate stable, moderate flow.

[c] Blood pressure stable, increased heart rate, heavy flow.

[d] Potent progestin: norgestrel or levonorgestrel.

and extent to which they interfere with work, relationships, and familial responsibilities. After the condition of PMS/PMDD is identified, the adolescent can be properly evaluated and educated about treatment options. Although various sources have advocated many different regimens for the management of PMS, no definitive findings have been reported, and no single effective treatment has been demonstrated. The overall goal of therapy is to improve the adolescent's quality of life by ameliorating the debilitating symptoms associated with PMS/PMDD.

Treatment involves education about the menstrual cycle and PMS, supportive self-care to reduce stress and the severity of symptoms, lifestyle modifications (eg, increasing exercise), dietary supplementation, and the initiation of specific medications (eg, selective serotonin reuptake inhibitors [SSRIs]) for severe PMS/PMDD symptoms. For example, therapies for mild to moderate symptoms include diet modification for the patient whose primary symptom is bloating, promotion of regular aerobic exercise, education about menstrual physiology and the relationship of changing hormones to symptoms, stress management, and cognitive-behavior therapy or group therapy. Calcium supplementation (1,200 mg daily in divided doses) and vitamin D are the only evidence-based dietary modifications that have been shown to consistently improve symptoms. Other vitamin and mineral supplements as well as certain herbal preparations require more definitive research before their use can be recommended. Some therapies that historically had been used extensively also have been associated with undesirable outcomes, such as the development of peripheral neuropathy with pyridoxine (vitamin B_6) at high doses.

Although it might be assumed that ovulatory suppression with COCPs in a conventional 21-day active/7-day placebo regimen would decrease PMS symptoms, their use has in fact been associated with incomplete suppression of ovulation and an exacerbation of PMS symptoms during hormone withdrawal. Lower estrogen dosing (eg, 20 mcg ethinyl estradiol), the use of the progestin drospirenone, and extended or continuous cycling of COCPs have been shown to reduce PMS symptoms in adult women with PMDD versus controls.

When mood symptoms predominate and significantly impair function, SSRIs are considered first-line treatment in adult women; however, this is not the case for teenagers. Fluoxetine, sertraline, and paroxetine are the only US Food and Drug Administration–approved SSRIs for use in the management of severe PMS/PMDD. Although fluoxetine is approved for use in children and adolescents, it is approved for only 2 conditions: major-depressive disorder and obsessive-compulsive disorder. Therefore, the decision to prescribe an SSRI in an adolescent with severe PMS/PMDD is at the discretion of the health professional because studies specific to adolescents are lacking and use of an SSRI in this age group requires diligent monitoring by a multidisciplinary team. Anxiolytic agents, specifically alprazolam, generally are not used in adolescents because of the possible development of drug dependency.

Vaginitis

See Chapters 59 and 60 for a discussion of the management of vaginal discharge in adolescents.

Prognosis

Most adolescents with common menstrual symptoms who receive aggressive, appropriate care are usually symptom-free after 3 to 4 months of continuous therapy. Complications associated with oral contraceptive use and NSAIDs are rare in this otherwise healthy patient population. Symptoms associated with an immature hypothalamic-pituitary-ovarian axis, such as anovulatory bleeding and abnormal uterine bleeding, may also resolve spontaneously but generally respond favorably to hormonal management. The prognosis for the adolescent with amenorrhea depends in part on the underlying etiology.

CASE RESOLUTION

More information should be obtained to exclude the numerous other causes of abnormal uterine bleeding in the adolescent before a diagnosis of anovulatory uterine bleeding can be made. Questions about breast tenderness, galactorrhea, weight loss, fatigue, visual changes, prolonged bleeding, and easy bruising can be particularly important. If the adolescent has no other symptoms, a hemoglobin or hematocrit as well as a complete blood cell count and a pregnancy test should be performed. An endocervical, vaginal, or urine specimen should be sent for nucleic acid amplification testing for gonorrhea and chlamydia. Depending on the severity of anemia and the desire for contraception, the adolescent should be placed on twice-daily iron supplementation and oral combined hormonal therapy for at least 3 months.

Resource

Center for Young Women's Health: https://youngwomenshealth.org

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CHAPTER 62

Disorders of the Breast

Monica Sifuentes, MD

CASE STUDY

A 2-year-old girl is brought to the office for bilateral breast swelling first noticed 3 weeks previously by her mother. The swelling is nontender and does not appear to be increasing in size. No history exists of galactorrhea. The child is otherwise healthy, takes no medications, and is not using any estrogen-containing creams or other over-the-counter products or supplements.

On physical examination, vital signs are normal, and the child is at the 50th percentile for height and weight. A 1.5-cm, firm, nontender mass is palpated below her left nipple. Below the right nipple, a 1-cm, nontender mass of similar consistency is present. There is no discharge from either nipple and no areolar widening. The abdomen is soft, with no masses palpated. The genitalia are those of a normal prepubescent female with no pubic hair and vaginal mucosa that appears red and not estrogenized.

Questions

1. What is premature thelarche, and how can it be differentiated from true precocious puberty?
2. What are the most common causes of breast hypertrophy in the infant?
3. When does pubertal breast development normally occur in females?
4. What are the most common causes of breast masses in adolescent females, and how should they be managed?
5. How can physiologic pubertal gynecomastia be differentiated from pathologic causes of gynecomastia in adolescent males?

Breast disorders occur in all pediatric age groups and can become a cause for significant concern for both patients and parents or guardians. A neonate may present to the pediatrician with bilateral breast hypertrophy and galactorrhea or mastitis. Bewildered parents or guardians might bring in their young prepubertal daughter because of what appears to be early breast development. An anxious adolescent female may notice for the first time that her breasts are asymmetric, or she may feel a lump beneath the skin. An adolescent male can present with unilateral or bilateral gynecomastia that makes him uncomfortable and causes severe psychological distress. Whatever the underlying cause, breast problems can be disconcerting at any age. Primary care physicians should be equipped to differentiate between normal variants of growth and pathologic conditions in newborns, infants, children, and adolescents. Significant disorders are rare, but diagnosis is important so that appropriate management can begin.

Epidemiology

Breast problems range from congenital anomalies and benign disorders related to hormonal stimulation to breast masses and tumors. Serious disorders, such as primary breast cancer, are exceedingly rare in children and adolescents, although inappropriate breast enlargement or gynecomastia as a sign of another neoplastic process is not uncommon.

Benign breast hypertrophy can occur in 60% to 90% of newborns and occurs in both male and female term neonates. Presentation may be unilateral or bilateral. Occasionally nipple discharge occurs, particularly in the case of well-intentioned family members who try to extract the milk, inadvertently promoting the central secretion of prolactin and oxytocin via breast stimulation.

Congenital anomalies of the breast include polythelia, polymastia, amastia, and athelia. *Polythelia*, or extra accessory nipples, can occur anywhere along the embryonic mammary ridge (also called the "milk line") from the axilla to the groin and occurs in 2% of the general population (Figure 62.1). Reportedly, abnormalities of the urologic and cardiovascular systems have been associated with polythelia. *Polymastia* refers to supernumerary breasts along the milk line and occurs less frequently than polythelia. The usual locations for supernumerary breasts are below the breast on the chest or the upper abdomen. Polythelia and polymastia may be familial and can occur bilaterally or unilaterally. Problems associated with breast development, such as a tuberous breast deformity, also can be thought of as a congenital anomaly, although it does not manifest until later in puberty when breast growth is noted to be underdeveloped or abnormal in appearance. The breasts have the appearance of a tuberous plant root, with an elevated inframammary fold, narrow breast base, and "herniation" of glandular tissue through the areolae, which are unusually large.

Amastia (congenital absence of glandular breast tissue) and *athelia* (absence of a nipple) are rare, but their presence often is associated with other anomalies of the chest wall, such as pectus excavatum. Amastia also is seen in Poland syndrome, which includes absence of the ipsilateral pectoral muscles, various rib deformities and upper limb defects (eg, syndactyly [webbed fingers]), and radial nerve aplasia (Figure 62.2).

Premature thelarche is isolated unilateral or bilateral breast development in girls between 1 and 4 years of age without other signs of sexual maturation (eg, pubic hair, estrogenized vaginal mucosa, acceleration of linear growth). An estimated 60% of cases occur between 6 months and 2 years of age, and a diagnosis after 4 years of age is uncommon. In contrast, *precocious puberty* is the appearance of any sign of secondary sexual maturation before age 8 years in girls with a normal body mass index or age 9 years in boys. In young females, this involves breast or pubic hair development, and in males it involves pubic hair development or testicular enlargement. Despite well-documented ethnic variation among children, 7 years is considered the lower acceptable age limit for the onset of puberty in non-Hispanic black and Mexican American girls.

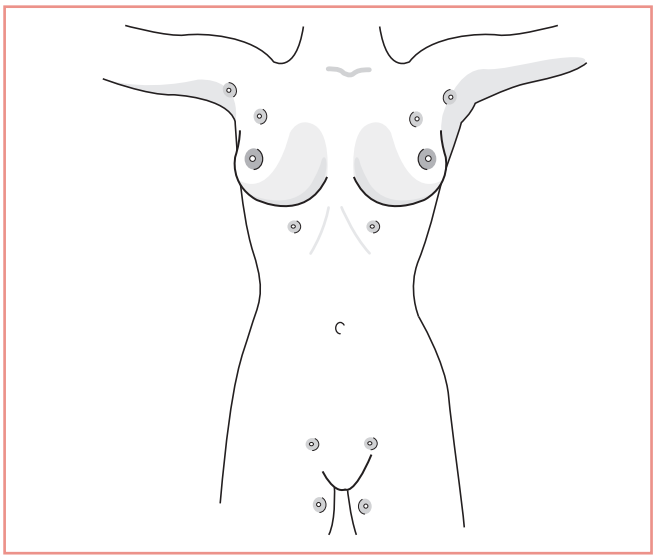

Figure 62.1. Polythelia. Supernumerary nipples along the embryonic mammary ridge (milk line).

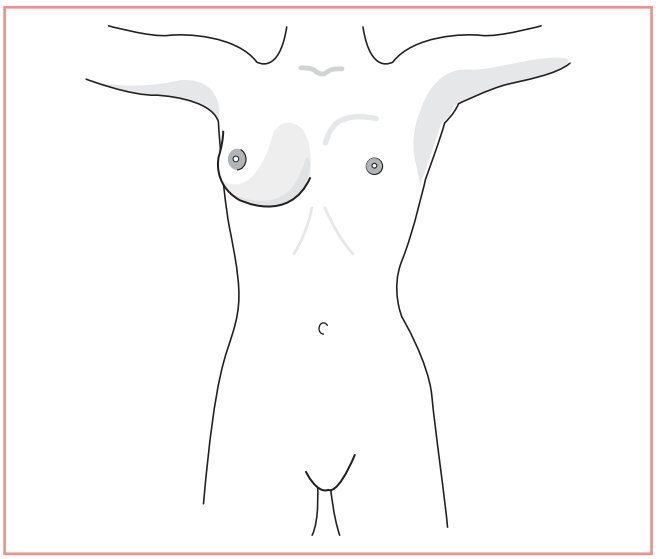

Figure 62.2. Amastia. Unilateral (left) complete absence of breast tissue.

Gynecomastia may occur in adolescent males as they progress through puberty and is often called "transient pubertal gynecomastia" or "physiologic pubertal gynecomastia." An estimated 60% to 70% of adolescent males are affected, with a peak incidence between ages 13 and 14 years or approximately 1 year after the onset of puberty. This generally corresponds to sexual maturity rating (SMR) (ie, Tanner stage) 3 to 4 genital and pubic hair development in the young male. Like breast development in the pubertal female, transient pubertal gynecomastia may be asymmetric and painful, although concurrent or sequential involvement of both breasts can occur. It is uncommon for pubertal gynecomastia to occur beyond age 17 or 18 years in the adolescent male.

In the adolescent female, breast masses are not uncommon; however, clinically significant lesions are rare. Breast cancer has an estimated annual incidence of 0.1 in 100,000 adolescents. In most studies of patients through age 20 years, the most common benign breast tumor is a fibroadenoma, which has been reported in 60% to 95% of biopsied lesions. Two-thirds of these lesions are located in the lateral quadrants of the breast, with most in the upper outer quadrant. The peak incidence of these lesions is in late adolescence (17–21 years of age), and they tend to occur more commonly in black females. Reportedly, 10% to 15% of cases are bilateral. Additionally, 25% of cases involve multiple fibroadenomas.

Fibrocystic changes are the second most common histologic diagnosis after fibroadenomas. Other breast masses include solitary cysts, abscesses, lipomas, and the *phyllodes tumor* (also known as *cystosarcoma phyllodes*), an extremely rare, rapidly growing, painless breast tumor that is nearly always benign and clinically can be confused with fibroadenoma, except for its aggressive growth. If malignant, however, cystosarcoma phyllodes can metastasize hematogenously to the lungs.

Malignancy is reported in less than 1% of excised lesions. Fewer than 50 cases of primary breast cancer in children and adolescents have been reported in the literature to date. Rhabdomyosarcoma and fibrosarcoma are among the other rarely reported primary tumors of the breast in adolescents. Metastatic cancer of the breast is more common than primary breast cancer and has been reported in children with primary hepatocellular carcinoma, leukemia, Hodgkin and non-Hodgkin lymphoma, neuroblastoma, and rhabdomyosarcoma. Of note is the increased lifetime risk for radiation-induced breast cancer in girls and adolescents who undergo mantle/chest wall irradiation during peak breast development (10–16 years of age); such irradiation typically is administered during treatment for Hodgkin lymphoma. The breast cancer risk for women who are survivors of Hodgkin disease is 75 times that of the general population. According to the literature, the cumulative risk for breast cancer during their lifetime exceeds 40% for girls who undergo chest irradiation for treatment of Hodgkin lymphoma.

Normal Breast Development

In the adolescent female, the first sign of puberty is breast development or thelarche. This begins with the appearance of a breast bud beneath the areola. Under the influence of estrogen, there is an increase in the adipose tissue along with the beginning of ductal and stromal growth. Progesterone initiates alveolar budding and lobular growth and contributes to the development of secretory lobules and alveoli. The alveoli are later lined by milk-secreting cells under the influence of prolactin when full maturation occurs during the first pregnancy.

The normal progression of breast growth is divided into 5 stages or SMRs. These descriptions are used to follow normal breast development, which occurs in parallel with and generally precedes pubic hair development. It usually takes 2 to 4 years for the completion of breast development, although, as in all aspects of puberty, variations do occur. The practitioner should keep in mind that many females remain in SMR 3 or 4 breast development until pregnancy. Additionally, especially between SMR 2 and 4, significant breast asymmetry can be quite common in the adolescent without indicating a pathologic process. After both breasts are fully mature and reach SMR 5, adequate catch-up growth usually has occurred.

Clinical Presentation

Neonates with breast disorders usually present in the first few weeks after birth with bilateral breast enlargement that may be asymmetric (Box 62.1). They may present with associated clear or cloudy nipple discharge. If an infection is present, the overlying skin may be warm and erythematous. Fever or other nonspecific symptoms, such as poor feeding and irritability, also may be present because mastitis involves the entire breast bud; although rare, septicemia can occur as well.

In prepubertal females, benign premature thelarche presents as unilateral or bilateral nontender subareolar swelling without the appearance of other secondary sexual characteristics. In contrast, girls with precocious puberty may have axillary hair, nipple and areola enlargement and thinning, and pubic hair in addition to early breast development. Adolescent females with a breast problem often report a unilateral breast lump noted incidentally by the teenager. It may be tender, fluctuant, firm, rubbery, or nodular. The adolescent also may report painful breasts (*mastalgia*) that can be cyclic in nature. For most breast masses, the overlying skin is normal, but occasionally skin changes do occur. Rarely, an associated nipple discharge may be present.

Because most breast masses occur in females, gynecomastia is particularly anxiety provoking in young adolescent males. It usually appears as a unilateral or bilateral 2- to 3-cm firm mass beneath the areola, which may or may not be tender. Irritation of the skin of the nipple may occur resulting from prolonged friction from clothing. Galactorrhea rarely accompanies pubertal gynecomastia and may be indicative of self-stimulation; illicit drug use, including cannabis, opiates, benzodiazepines, and amphetamines; or exposure to other medications, such as risperidone.

Box 62.1. Diagnosis of Breast Disorder From Birth Through Adolescence

Neonates, Infants, Prepubescent Children, and Adolescent Males

- Unilateral or bilateral subareolar mass
- Possible associated nipple discharge
- Overlying skin changes, such as erythema in neonates and infants

Adolescent Females

- Firm, rubbery, freely movable mass
- Possible tenderness
- Breast asymmetry
- Skin changes, such as shininess, venous distention, or dimpling (rare)
- Possible associated nipple discharge

Pathophysiology

Neonatal breast hypertrophy seemingly is a response to maternal estrogen exposure in utero. Constant stimulation can result in persistent swelling, galactorrhea, and overt infection (ie, mastitis). Of note, if galactorrhea is present, it should not persist beyond the first few weeks after birth. Generally, preterm neonates are less responsive to maternal hormones and, therefore, breast hypertrophy occurs less often in this age group and its appearance may be delayed for weeks.

Benign premature thelarche is a variation of normal pubertal development with transient elevations in estrogen levels from functional ovarian cysts or fluctuations in pituitary gonadotropin secretion. Often, the breast enlargement occurs without other estrogen effects, such as an increase in uterine size or changes in the appearance of the external genitalia. Typically, no linear growth or bone age advancement is associated with this condition. Current research is examining the potential role of leptin and its influence on sex steroids in the development of premature thelarche as well as pubertal gynecomastia.

Central precocious puberty is the result of early activation of the hypothalamic-pituitary-gonadal axis and the secretion of gonadotropin-releasing hormone (GnRH)-dependent pituitary gonadotropins in a pulsatile pattern. Although a search may be undertaken for an underlying central nervous system (CNS) or gonadal abnormality, most cases in females are idiopathic. In contrast, less than 10% of males with precocious puberty do not have an identifiable cause, and it has been reported that approximately 50% of boys with precocious puberty have an identifiable intracranial process. Central nervous system tumors cause precocious puberty by impinging on the neuronal pathways that inhibit the GnRH pulse generator in childhood. Cranial irradiation, received as a part of tumor therapy, also can cause central sexual precocity. Pseudo-precocious puberty is GnRH-independent and is caused by the extrapituitary secretion of gonadotropins or the secretion of gonadal steroids independent of pulsatile GnRH stimulation. (See the article by Long in Selected References for a general review of precocious puberty.)

The cause of fibroadenomas in adolescent females is postulated to be an abnormal sensitivity to estrogen. Observations supporting this hypothesis include the presence of estrogen receptors in the tumor and an increased incidence of this type of tumor during late adolescence. Thus, prolonged exposure to estrogen may play a role in the development of fibroadenoma. Enlargement can occur during pregnancy or toward the end of the menstrual cycle.

The definition of *gynecomastia* is an increase in the glandular and stromal tissue of the male breast. Physiologic gynecomastia is thought to occur from a transient imbalance between estrogen and androgens during puberty. Alterations in the ratio of these hormones results in an increase in estrogen relative to testosterone. Certain medications can cause elevations in serum prolactin and lead to gynecomastia or galactorrhea (Box 62.2). Some illicit drugs, such as marijuana, contain phytoestrogens that can mimic estrogen or stimulate estrogen receptor sites. Specific medications, such as spironolactone and cimetidine, interfere with androgen receptors or induce inhibition of enzymes necessary for steroid synthesis.

Differential Diagnosis

The differential diagnosis of breast disorders in children and adolescents depends on sex and age at onset. In addition, the presence or absence of other secondary sexual characteristics is helpful to differentiate between a variation of normal pubertal development and a pathologic process.

Infants and Children Younger Than 9 Years

In prepubertal children, the differential diagnosis of isolated early breast development includes exposure to exogenous sources of estrogen, such as skin creams that may contain tea tree or lavender oil, makeup, and medications (eg, oral contraceptives).

Box 62.2. Causes of Galactorrhea

- Mechanical stimulation of the nipple
- Medications
  - Opiates
  - Estrogens
  - Digitalis
  - Butyrophenones (haloperidol)
  - Phenothiazines
  - Risperidone
  - Metoclopramide
  - Isoniazid
  - Reserpine
  - Cimetidine
  - Benzodiazepines
  - Tricyclic antidepressants
- Illicit drugs
  - Marijuana
  - Heroin
- Hypothalamic-pituitary disorders

For patients with suspected precocious puberty, other etiologies must be considered in addition to exogenous hormones (Box 62.3). Central nervous system tumors, lesions, and vascular insults are among the most common causes. Congenital tumors, such as hypothalamic hamartomas, are especially important to rule out because they often present before age 3 years. Other CNS tumors to consider are neurofibromas, optic gliomas, astrocytomas, and ependymomas. Specific CNS lesions include cysts in the area of the third ventricle and congenital brain defects. Hydrocephalus, postinfectious encephalitis or meningitis, head trauma, and static cerebral encephalopathy also can cause sexual precocity. Endocrine disorders include primary hypothyroidism, estrogen-producing tumors of the ovary or adrenal gland, and ovarian cysts.

Adolescents

The differential diagnosis of breast masses in adolescent females is extensive (Box 62.4). Conditions can be distinguished from one another based on the location of the lesion; its texture, mobility, and size; and the speed at which it is enlarging.

Box 62.3. Differential Diagnosis of Precocious Puberty

- Central (true)—GnRH–dependent
- Idiopathic
- Central nervous system
  - Tumor
    - Optic and hypothalamic gliomas (often associated with neurofibromatosis), hypothalamic hamartoma, astrocytoma, ependymoma, craniopharyngioma
  - Lesion
    - Congenital defects, hydrocephalus, cyst in the third ventricle
  - Insult
    - Postinfectious encephalitis or meningitis, static encephalopathy
  - Infection
    - Abscess, tuberculous granulomas of the hypothalamus
  - Head trauma
  - Sequela of cranial radiation
  - Sarcoid granuloma
- Endocrine
  - Hypothyroidism
  - Secondary to GnRH-independent precocious puberty (21-hydroxylase deficiency, Albright syndrome)
  - Peripheral (pseudo-)—GnRH-independent
  - Adrenal
    - Tumor
    - 21- or 11-hydroxylase deficiency
- Gonadal
  - Tumor
    - Albright syndrome
    - Familial testotoxicosis
  - Ectopic human chorionic gonadotropin–secreting tumor
  - Exogenous steroids

Abbreviation: GnRH, gonadotropin-releasing hormone.

Box 62.4. Causes of Breast Masses in the Adolescent Female

- Fibroadenoma
- Breast abscess
- Breast cyst
- Juvenile (giant) fibroadenoma
- Cystosarcoma phyllodes (benign)
- Fat necrosis (secondary to trauma)
- Lipoma
- Hematoma
- Intraductal papilloma
- Adenocarcinoma
- Rhabdomyosarcoma
- Angiosarcoma
- Lymphoma
- Cystosarcoma phyllodes (malignant)

According to some authors, gynecomastia can be classified as type 1, 2, or 3 based on physical examination findings. Type 1 is consistent with benign pubertal hypertrophy. The differential diagnosis for types 2 and 3 includes physiologic gynecomastia (no evidence of an underlying disease process); organic disorders, such as hyperthyroidism, liver disease, and testicular or adrenal neoplasms; rare genetic syndromes, such as Klinefelter syndrome; and side effects of certain prescription medications, over-the-counter supplements, or drugs of abuse (Box 62.5).

Persistent galactorrhea can be caused by several conditions in addition to excessive stimulation of the nipple from sexual activity or constant friction to the area. Other etiologies include neurologic, hypothalamic, pituitary, and endocrine disorders. Common causes in the adolescent female are prolactin-secreting tumors and hypothyroidism. The same drugs that induce galactorrhea in females can cause gynecomastia in males (see Boxes 62.2 and 62.5).

Evaluation

History

In the infant or child, the history should focus on endogenous as well as exogenous sources of estrogen (Box 62.6). Additionally, it is important to ascertain from the parent or guardian whether a growth spurt has occurred as well as if other physical features of puberty have appeared. With teenagers, it is important to inquire about medications; complementary and alternative therapies, including herbal remedies, supplements, and illicit drug use; and a history of systemic illness. All adolescent patients should be interviewed alone, especially when discussing illicit substance use (see Chapter 63). The adolescent male may feel particularly embarrassed and self-conscious given the nature of his visit; thus, the physician should be especially patient and supportive during both the interview and the physical examination.

Box 62.5. Causes of Type 2 Gynecomastia in the Adolescent Male

- Idiopathic
- Hormone-secreting tumors
  - Seminomas (account for 40% of germ cell tumors)
  - Leydig cell tumor
  - Teratoma
  - Feminizing adrenal tumor
  - Hepatoma
  - Bronchogenic sarcoma (ectopic human chorionic gonadotropin production)
- Thyroid dysfunction (hyperthyroidism and hypothyroidism)
- Renal failure and dialysis
- Chronic liver disease/cirrhosis of the liver
- Klinefelter syndrome (XXY)
- Testicular feminization syndrome (partial androgen insensitivity syndrome)
- Drugs (prescription medications and substances of abuse)
  - Marijuana, amphetamines, heroin, methadone
  - Alcohol
  - Anabolic steroids/androgens
  - Estrogens, testosterone
  - Growth hormone
  - Cimetidine, ranitidine
  - Omeprazole
  - Digitalis
  - Spironolactone
  - Phenytoin
  - Tricyclic antidepressant agents
  - Anxiolytic agents: diazepam, buspirone
  - Risperidone
  - Selective serotonin reuptake inhibitors
  - Cancer chemotherapeutic agents: alkylating agents, methotrexate
  - Isoniazid
  - Ketoconazole
  - Highly active antiretroviral treatment
- Over-the-counter herbal supplements or skin care products containing lavender, tea tree oil, or other oils with estrogen-like actions
- Pseudogynecomastia (adipose tissue in male with obesity)

Physical Examination

The physical examination includes an assessment of the patient's linear growth, especially in cases of suspected precocious puberty. The height and weight should be plotted on the growth curve and compared with previous measurements. Accelerations in height occur in sexual precocity. Excessive weight gain also should be noted; obesity can simulate breast enlargement in young females and gynecomastia in males, and adipose tissue can be mistaken for breast development if the tissue is not palpated correctly.

The extent of the breast examination depends on the age of the patient. In infants and young children, the breast tissue should be

Box 62.6. What to Ask

Breast Disorder

Prepubertal Children

- At what age was the breast mass first noted?
- Does it seem to be increasing in size?
- Is it tender or erythematous?
- Is there associated discharge from the nipple?
- Has the child been exposed to any estrogen-containing skin creams, medications, or other products?
- Is the child or adolescent using any herbal supplements, such as ginseng or fennel, or products that contain tea tree or lavender oil?
- In the male patient, is he taking any medications known to cause gynecomastia, such as digoxin, omeprazole, or isoniazid?
- Is the child experiencing any neurologic symptoms, such as headache, ataxia, or visual disturbance?
- Is there a history of head trauma, central nervous system infection, or cerebral insult?
- Has the parent noted any other signs of early pubertal development (eg, pubic hair, acne, sudden increase in height)?

Adolescent

- When was the breast mass first noticed, and where is it located?
- Does it seem to be increasing in size?
- Is the lesion tender?
- Is there a history of trauma to the breast?
- Is there any discharge from either nipple?
- In the female, when was the last menstrual period?
- Is there a history of headache or visual disturbances?
- Are there any signs or symptoms of systemic illness, such as weight loss?
- Is there a family history of breast cancer in a first-degree relative, particularly the mother? If so, what was her age at diagnosis?
- Is there a history of chest wall radiation or treatment with chemotherapeutic agents?
- In the male, is he taking any medications that can cause gynecomastia, such as cimetidine?
- Is the adolescent male using anabolic steroids, supplements, or topical oils?
- Is the adolescent using any other illicit substances, such as marijuana or heroin?
- Is there a family history of gynecomastia or abnormal sexual development?

measured and the size recorded so that growth can be monitored over time. Consistency of the tissue and mobility also should be evaluated. Breast growth as a result of neonatal breast hypertrophy and benign premature thelarche is nontender, firm, and freely mobile. The nipple should be examined for a clear or cloudy discharge by gently compressing each nipple separately.

In the adolescent female, the breast examination should include visual inspection of the breasts as well as palpation of any lesions and axillary nodes. Ideally, this would be performed in the sitting and supine positions, as is done in adult women. Most adolescent females, however, may be uncomfortable with so extensive an examination. The physician must take the time to explain the reasons for the examination to help the patient feel less self-conscious. All physicians and other health professionals should ensure that a female staff member is present to chaperone during the breast examination.

Visual inspection should assess for SMR, appearance of the skin, breast symmetry, and evidence of trauma. Shiny skin or superficial venous distention on 1 breast would indicate the possible presence of an underlying large mass. A peau d'orange (ie, orange peel) appearance of the skin or erythema and warmth should be noted as a sign of an infiltrative lesion or infection, respectively.

Palpation of the breast mass can be accomplished with the patient in the supine position using 1 of 3 methods. Using the second, third, and fourth fingers of 1 hand, the examiner should gently palpate each breast in a pattern of concentric circles, spokes of a wheel, or vertical and horizontal lines. The location of the mass should be noted; a mass beneath the areola might indicate an intraductal lesion, whereas the upper outer quadrant is the classic location for a fibroadenoma. The consistency of the lesion is important. Is it firm, rubbery, and fluctuant, or irregular and lumpy? Is it freely movable or attached to the chest wall? Fibroadenomas tend to be nontender, firm, discrete, freely movable, and rubbery. A tender, poorly defined mass is consistent with a contusion; a hematoma is more sharply defined with associated skin ecchymoses. Fat necrosis can occur after trauma and is painless, firm, well circumscribed, and mobile. The size of the mass should be measured and recorded. It is important to remember that tumor size does not generally correlate with malignant potential. Tender, diffuse, cord-like thickening, which may feel like a beanbag, may be indicative of fibrocystic breast changes. The mean age at presentation of fibrocystic breast changes is mid-adolescence. This condition may involve 1 or both breasts, is more apparent around the time of menses, and may be exacerbated by the consumption of caffeinated beverages. Limiting caffeine consumption may provide symptomatic relief. Finally, each nipple should be gently squeezed to check for a discharge. If present, whether it is clear, milky, or bloody should be noted. A serosanguineous or sanguineous discharge is indicative of an intraductal mass. Additionally, a retracted nipple is indicative of involvement of the areolar area.

In the adolescent male, the breast tissue should be gently palpated in the supine position to distinguish between fat deposition without glandular proliferation in the overweight patient (ie, pseudogynecomastia, adipomastia) and true gynecomastia. Type 1 gynecomastia presents as a unilateral or bilateral freely mobile subareolar nodule, which is generally up to 3 cm in size. Enlargement beyond the areolar perimeter is consistent with type 2 gynecomastia. Type 3 resembles SMR 3 breast development in girls. The breast tissue associated with types 1 and 2 also is firm and rubbery and may be tender to palpation, whereas type 3 has a consistency similar to female breast tissue.

The examiner should palpate for axillary lymphadenopathy. Although most physicians associate it with breast cancer, it also may be found with infection or necrosis of a benign tumor. In the

adolescent male, in addition to palpation of the breast tissue, it is important to evaluate liver size and texture as well as define the SMR of the genitalia to determine whether pubertal development is consistent with the gynecomastia. The testicles should be palpated carefully for size and consistency and the presence of masses, nodules, or asymmetry. Any evidence of atrophy (ie, decrease in testicular size) should be noted. Additionally, findings suggestive of hypothyroidism or hyperthyroidism, liver disease, or other stigmata suggestive of a syndrome must be investigated.

A detailed neurologic examination, including examination of the fundi, should be performed—especially in children with sexual precocity—to confirm or detect a CNS disorder.

Laboratory Tests

The laboratory workup for breast disorders is dictated by the findings on history and physical examination. Isolated neonatal breast hyperplasia and premature thelarche require no laboratory studies. Although serum gonadotropin concentrations (ie, luteinizing hormone, follicle-stimulating hormone) and estradiol levels can be obtained in girls with precocious puberty, definitive demonstration of an activated hypothalamic-pituitary axis generally requires the administration of a GnRH stimulation test by a pediatric endocrinologist. In addition, a morning testosterone level should be ordered in boys. Based on these results, further studies may be indicated, such as a serum human chorionic gonadotropin (hCG) level.

For most breast lesions in adolescent females, no laboratory studies are needed. Ultrasonography-guided fine-needle aspiration of the mass may be performed in patients with an apparent discrete collection of fluid. The aspirated fluid should be sent for culture and antibiotic sensitivities. Sometimes, to relieve patient and parental anxiety or to better identify the etiology of the mass, it is necessary to perform another procedure (eg, core needle biopsy) if imaging features are atypical or the lesion has undergone rapid growth. Excisional biopsy of the mass allows for more accurate histologic information but is rarely indicated for most lesions.

In the healthy adolescent male with gynecomastia and no evidence of systemic illness, no history of medication use or illicit substance abuse, and an otherwise normal physical examination (including the testicular examination), no further laboratory studies are necessary. If pubertal gynecomastia and other systemic illnesses are ruled out, an endocrine workup is appropriate to elucidate the cause of nonpubertal gynecomastia. This should begin with morning serum levels of hCG, luteinizing hormone, follicle-stimulating hormone, and serum testosterone and estradiol because circadian variation may affect their interpretation. Dehydroepiandrosterone sulfate, thyroid function tests, renal function studies, and liver enzymes also may be useful. If these laboratory studies are normal, the diagnosis is idiopathic gynecomastia. If they are abnormal, consultation with a pediatric endocrinologist or adolescent medicine specialist should occur.

A pregnancy test and serum prolactin level should be ordered in the adolescent female with galactorrhea, regardless of the menstrual history.

Imaging Studies

Left hand and wrist radiographs to determine the child's bone age should be obtained in children with a diagnosis of precocious puberty. Additionally, magnetic resonance imaging of the brain should be obtained in boys to evaluate for a CNS lesion or structural abnormality in the hypothalamus or pituitary gland. Depending on the history, magnetic resonance imaging may be indicated in some girls. Pelvic ultrasonography, although rarely necessary, can be performed to rule out the presence of an ovarian tumor or cyst in girls with precocious puberty.

Mammography is not recommended as part of the evaluation of a breast mass in the pediatric age group. Particularly in female adolescents, mammograms can be very difficult to interpret because of the dense fibroglandular breast tissue, which reduces the overall sensitivity of the examination. Exposing developing breast tissue to ionizing radiation and the associated cellular changes that may result in future malignancy is also a consideration. Additionally, the risk for primary breast cancer in an otherwise healthy adolescent girl with no risk factors is extremely low. Breast ultrasonography is generally the primary imaging modality for the evaluation of a breast mass for several reasons. It accurately confirms the presence of the mass and helps distinguish between a cystic lesion and a solid mass. Ultrasonography is noninvasive and causes no pain for the anxious teenager. It can also provide more accurate measurement of the size of the lesion and its location prior to an image-guided biopsy. Finally, specific characteristics of the lesion, such as the shape, margins, and presence of microcalcification, can help differentiate benign and malignant lesions.

Testicular ultrasonography to search for a tumor is indicated in the adolescent male if the level of serum hCG or estradiol is elevated or if a testicular mass is noted on physical examination. Other imaging studies for the evaluation of gynecomastia generally are not useful.

Management

In neonates, mastitis most often is caused by *Staphylococcus aureus* and group B streptococcus. Gram-negative bacilli also have been reported. Parenteral antibiotics should be initiated when the diagnosis is made. Incision and drainage of a breast abscess is rarely indicated and should only be undertaken by an experienced surgeon familiar with the anatomy of the breast to minimize the likelihood of injury to the affected breast bud.

Congenital anomalies, such as polythelia and polymastia, do not require any treatment. If, however, the patient or parent/guardian wants the tissue removed for aesthetic or psychological reasons, it is recommended to do so before puberty. Reconstructive surgery for amastia, as in Poland syndrome, is typically delayed until late adolescence to allow full development of the unaffected breast.

Although no treatment is required for benign premature thelarche, parents and guardians need to be reassured that the condition is self-limited. The patient should be reexamined periodically to check for any further progression of puberty, such as persistent breast growth, the appearance of pubic hair, or a growth spurt.

If no underlying medical condition has been discovered, the treatment for most children with central precocious puberty is directed at controlling the secondary sexual development with GnRH agonists/analogue therapy. When GnRH is administered on a routine basis or continuously, gonadotropin secretion decreases, which delays further pubertal development. Leuprolide acetate is the GnRH agonist most often prescribed in the United States. Children should be followed every 1 to 3 months in conjunction with a pediatric endocrinologist to monitor their progression and response to therapy. The child continues to receive the medication until they reach the normal age of puberty, at which point the medication is discontinued and the process of puberty begins again.

Unless otherwise indicated by the type of tumor, children with a CNS lesion as a cause of precocious puberty usually do not require neurosurgical intervention. Therapy should focus on minimizing the degree of growth acceleration and the development of secondary sexual characteristics.

Most breast masses in adolescent females are small, well demarcated, firm or rubbery, and nontender and can be managed with the "wait and watch" approach. The patient should be followed every 3 to 4 months, preferably allowing a few menstrual cycles to pass between each visit. If there is no change in the lesion or just a small increase in its size, no studies or procedures are indicated because it is most likely a fibroadenoma. As previously noted, a core needle biopsy may be requested to relieve the anxiety for the parent/guardian and the teenager that accompanies the presence of a breast lesion and to confirm the diagnosis. Total excision of the tumor mass and a careful histologic evaluation may be warranted in some cases, especially if the mass is painful or rapidly enlarging and exceeds 3 cm; however, excision is unnecessary in most instances. According to the literature, if findings on physical examination, imaging, and biopsy are consistent with a benign lesion, the diagnosis of a benign mass can be made with 99% accuracy. If this is the case, no further procedures are indicated and follow-up with the patient every 6 months to 1 year is sufficient. Surgical removal of a tumor that progressively enlarges over several months (eg, giant fibroadenoma) is important. This type of fibroadenoma is greater than 5 cm in size at onset or appears soon after menarche and accounts for 4% to 10% of fibroadenomas of the breast. When the lesion becomes very large, an acceptable cosmetic result is more difficult. Accordingly, surgical removal of a giant fibroadenoma shortly after the time of diagnosis rather than watchful waiting is warranted. It is important to note that any adolescent patient with a palpable breast mass and a past history of malignant disease or family history of breast cancer should be evaluated aggressively and referred to a pediatric surgeon or breast surgeon directly for a diagnostic excisional biopsy.

The primary treatment for physiologic pubertal gynecomastia, or type 1, is reassurance for the adolescent male and his family that the condition is self-limited in 75% to 90% of adolescents and should regress spontaneously within 1 to 2 years, although some sources report up to 3 years. In most cases, the boy should be reexamined periodically (ie, every 6 months) until resolution occurs. Type 2 gynecomastia may require surgical reduction of the mammary gland, although some studies have shown success with medical therapy. The off-label use of 10 to 20 mg of tamoxifen orally twice daily for 3 months has been shown in some cases to decrease breast tenderness and pain, followed by a decrease in breast tissue. Surgical intervention may be warranted after a period of observation for at least 12 months in cases of nonobese males with intractable breast pain or tenderness, persistent breast growth, and/or significant psychological distress. Surgery currently involves a combination of ultrasonic liposuction and direct excision of the breast tissue beneath the nipple and areola. The adolescent male may benefit from concurrent psychological counseling as well.

Other underlying causes for gynecomastia should be treated accordingly, and any drugs or medications contributing to the condition or associated galactorrhea should be discontinued, if possible.

Prognosis

The prognosis of a breast disorder in the child or adolescent depends on the particular lesion. Generally, most lesions, such as neonatal breast hyperplasia and premature thelarche, are self-limited and resolve spontaneously. Breast development persists for 3 to 5 years in 50% of cases of premature thelarche, but in 1 retrospective study, most cases regressed within 6 months to 6 years after the diagnosis. Aside from the short stature that may accompany idiopathic central precocious puberty, these females also tend to have a good prognosis. Fibroadenoma in the adolescent female can recur but typically is benign and has no direct association with the development of breast cancer. Most cases of pubertal gynecomastia in adolescent males resolve within 1 to 3 years.

CASE RESOLUTION

The child has a diagnosis of premature thelarche. She has no known exposure to exogenous sources of estrogen or alternative therapies that are associated with breast growth and has isolated breast tissue development with no other secondary signs of pubertal maturation. Her parents should be informed of this diagnosis and reassured that the condition is self-limited and does not indicate that the child is starting puberty. The child should be scheduled for a follow-up visit in 3 to 4 months to remeasure the breast buds and reexamine the genitalia for the appearance of pubic hair as well as to monitor the patient's linear growth.

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CHAPTER 63

Substance Use/Abuse

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CASE STUDY

A 17-year-old male is brought to your office by his father with a chief report of chronic cough. You have followed this patient and his siblings for several years and know the family quite well. The father appears very concerned about "this cough that just won't go away." The adolescent is not concerned about the cough, however, and reports no associated symptoms, such as fever, sore throat, chest pain, or sinus pain. You ask the father to step out of the room for the rest of the interview and the physical examination.

On further questioning, the patient reports that he vapes (ie, smokes electronic cigarettes) daily and has tried marijuana as well as cocaine. He denies regular use of these substances but reports exposure to these drugs at parties and when he spends time with "certain friends." The adolescent is now in the 11th grade, attends school regularly, and thinks school is "OK." His grades are average to above average, but he thinks he might fail 1 class this semester. Although he formerly played baseball, he stopped last year. He hopes to get a part-time job at a local fast-food restaurant this summer. Currently, he is sexually active with only females of his age and uses condoms occasionally. He denies suicidal ideation and exposure to any firearms.

On physical examination, he appears healthy with an occasional dry cough. He is afebrile, and his respiratory rate, heart rate, and blood pressure are normal. Pertinent findings on examination include slight conjunctival injection bilaterally, nasal turbinate erythema and edema, and mild erythema of the posterior pharynx. The patient is negative for tonsillar hypertrophy. The remainder of the examination is within normal limits.

Questions

1. What are the most common manifestations of substance use/abuse in adolescents?
2. What are the risk factors associated with substance use/abuse in adolescents?
3. What other conditions must be considered when evaluating adolescents with a history of chronic substance use/abuse?
4. What laboratory evaluations, if any, should be performed for the adolescent with suspected substance use/abuse?
5. What are the specific consequences of short- and long-term use/abuse of substances such as alcohol, marijuana, cocaine, opiates, and hallucinogens?

Primary care physicians are in a unique position to educate their patients, particularly young teenagers, about alcohol and substance use/abuse through primary prevention and anticipatory guidance. Ideally, this should begin before the teenager has first tried a cigarette or alcoholic drink, with the physician gradually introducing each topic as the preteen enters middle school and becomes accustomed to speaking to his, her, or their physician alone. Opportunities for education include health maintenance visits, the preparticipation sports physical evaluation as the teenager enters high school, and medical encounters for an acute injury or illness. More importantly, if a primary care physician is fortunate enough to have a long-standing relationship with the teenager, the physician can identify, evaluate, and manage a substance use disorder as soon as it develops and assist the patient and family proactively with appropriate referrals and local resources, thereby improving the adolescent's overall outcome.

Ideally, all preteen and adolescent patients would be questioned and counseled about the use of illicit substances, alcohol, and tobacco at each health maintenance visit (see Chapters 4 and 38). Unfortunately, this does not occur consistently because some health professionals do not feel comfortable opening that avenue of conversation or simply do not have the time and resources to inquire and intervene. Time constraints, unfamiliar billing codes, and difficulty maintaining confidentiality for sensitive services in a busy office or clinic make screening for substance use challenging. As a result, primary care physicians miss valuable opportunities to adequately assess adolescents for alcohol and substance use disorders and provide them with the necessary guidance to ensure their future health, safety, and well-being.

Substance use is use of or experimentation with illicit drugs, prescription medications, alcohol, or tobacco. Illicit drugs include marijuana; cocaine; amphetamines; hallucinogens, such as lysergic acid diethylamide (LSD), mescaline, and psilocybin, which is found in *Psilocybe mexicana* mushrooms; opiates; and phencyclidine hydrochloride (PCP). *Substance abuse* refers to the chronic use of mind-altering drugs despite adverse effects. *Addiction*, a chronic relapsing disorder, is the term applied to compulsive and continued use of a substance despite adverse consequences. Because addiction is neurologically based, the substance may produce physical dependence or symptoms of withdrawal when it is discontinued.

Epidemiology

Current Trends and Prevalence Rates

Adolescents in the United States currently use a wide range of substances. Alcohol, tobacco, and marijuana are by far the more common and most popular substances and can serve as gateway drugs to more serious illicit drug use. Several surveys tracking substance use/abuse among adolescents are conducted annually in the United States to identify the magnitude of high-risk behavior among those in 8th through 12th grade. The most well-known of these surveys are Monitoring the Future, which is administered annually to students in 8th, 10th, and 12th grade by the University of Michigan for the National Institute on Drug Abuse; the Youth Risk Behavior Surveillance System (YRBSS) survey, conducted biannually by the Centers for Disease Control and Prevention (CDC) of students in grades 9 through 12; and the National Survey on Drug Use and Health, a computer-assisted interview of residents 12 years and older conducted in the home. It is important to remember that most statistics do not include the estimated 15% to 20% of students who drop out of high school before their senior year.

In a 2017 survey of graduating high school seniors, approximately 60% admitted to alcohol use at some time during their life. Almost 30% of students reported drinking alcohol during the month preceding the survey. Binge drinking likely has contributed most to the overall morbidity and mortality associated with alcohol use in adolescents and young adults. Among high school seniors in the class of 2017, approximately 20% reported having 5 or more drinks in a row within a couple hours on at least 1 day during the 30 days before the YRBSS was administered. Although tobacco use among adolescents decreased from 1999 to 2017, data from the CDC indicate that in 2017 approximately 10% of teenagers nationwide reported current cigarette use and another 10% percent smoked at least one-half pack of cigarettes per day. Nationwide, the current rates of smokeless tobacco use (eg, chewing tobacco, snuff, dip) and cigar or cigarillo use are 6% and 8%, respectively. As expected, use of smokeless tobacco is much higher among males than females. Electronic vapor products (ie, electronic [e-] cigarettes, e-cigars, and e-pipes; vape pipes, vaping pens, hookahs), which were introduced in the US market in the middle of the first decade of the 21st century, have become the most commonly used tobacco product among youth in the United States, with many adolescents and young adults later transitioning to traditional cigarettes. In 2017 alone, greater than 40% of high school students reported ever having used an electronic vapor product. E-cigarette advertising aimed at teenagers and marketing strategies promoting flavored solutions have contributed greatly to the popularity of e-cigarettes among this age group. By 2019, there were an increasing number of reports of deaths related to vaping, and a number of states issued a ban on vaping product marketing, issued a ban on flavored vaping solutions, or withdrew vaping products from the market.

Marijuana is the most commonly used illicit psychoactive substance. In 1993, 35% of high school seniors reported ever having used marijuana; in 1997, this figure increased to greater than 50%. Per current estimates from the 2017 YRBSS, this figure is approximately 36%, with nearly 20% of high school seniors reporting marijuana use 1 or more times during the month preceding the survey. Daily use of marijuana has been reported in 6% of high school seniors.

The use of other substances among adolescents was generally on a downward trend in the late 1980s and early 1990s; however, use is once again on the rise. This phenomenon is known in the substance use/abuse literature as "generational forgetting," which occurs as acknowledgment of adverse effects of specific drugs fade over the years. Reportedly, approximately 9% of high school graduates in 1997 tried cocaine, with approximately 4% having used it in the previous month. These figures remained essentially unchanged until 2007, when cocaine use declined; currently, use of this substance is at an historical low of 1% among 12th-graders. The 1991 prevalence rate for LSD usage was 5%, and its use also remained stable over in the next 10 years until 2001, when the rate increased to 8% and became more widespread than cocaine use among high school students. According to the 2017 YRBSS survey, 9% of 12th-graders nationwide tried LSD or another hallucinogenic drug. Lifetime amphetamine use among 12th-graders was 3% in 2017, with a range of 2.3% to almost 8% across state surveys. Additionally, nationwide ecstasy use was reportedly approximately 4%.

Concurrently, the reported use of over-the-counter (OTC) nonprescription stimulants that contain caffeine has increased, with popular energy drinks now sold in many convenience stores and supermarkets. Other substances used to "get high," such as inhalants (eg, aerosol spray paints, hair sprays, paint thinners, whipped cream containers), are often used by younger students (ie, preteens) and unfortunately can be found in many garages, workrooms, and basements. Although the rate has decreased from 1997, in 2017 7% of early adolescents (ie, ninth graders) reported sniffing or inhaling substances to become intoxicated. Dextromethorphan also has become popular as an OTC product used/abused by adolescents secondary to its hallucinogenic effects and easy accessibility in cough syrups. Studies confirm an increasing trend in its use/abuse, particularly in teenagers younger than 18 years.

The nonmedical use/abuse of prescription drugs, such as Oxycontin, Percocet, Vicodin, Adderall, Ritalin, and Xanax, has increased more than that of most illicit drugs in the past 2 decades. Many teenagers report the ease by which prescription drugs can be obtained, resulting in continued use/abuse and future dependence as an adult. In 2017, nonmedical prescription drug use was reported by up to 17% of teenagers 1 or more times during their life. Certain prescription drugs, namely opioids, stimulants, sleeping pills, and anxiolytics, now represent the third most widely used/abused substance in adolescents after alcohol and marijuana.

Although not everyone considers them an illicit substance, anabolic steroids are used/abused by some adolescents, mostly males, to increase muscle size and strength. In 1997, approximately 3% of adolescent males admitted to using them at some time in their life. More recently, studies indicate as many as 5.5% of high school students participating in sports use anabolic steroids (6.6% males, 3.9% females). The 2017 nationwide figure per the CDC is almost 3%; however, state and local surveys indicate a range of 2% to 7% for use of anabolic steroids.

Demographics

Generally, adolescent males use illicit drugs more than females do, with a few exceptions. Males are more likely to use anabolic steroids, but females reportedly use amphetamines, barbiturates, tranquilizers, and OTC diet pills more than their male counterparts. Additionally, although annual prevalence rates for overall alcohol use show little difference by sex, adolescent males have a higher rate of heavy or binge drinking compared with adolescent females. Tobacco usage is essentially the same for both sexes, except for smokeless tobacco and cigars, with more boys using these products.

Adolescents who do not plan to attend college are more likely to use illicit substances than their college-bound counterparts, and these adolescents and young adults also are more likely to use illicit drugs more frequently. No difference between the 2 groups exists, however, in the rates of ever having tried illicit substances. Binge drinking also continues to escalate among older adolescents and young adults attending college. The specific influence of parental education, socioeconomic status, and race or ethnicity on the use/abuse of illicit substances is difficult to determine because many other factors, such as genetics and the environment, contribute to heavy drug use and addiction.

Risk Factors and Behaviors

Although alcohol and tobacco are considered licit or lawful drugs, it is illegal for minors to purchase and use alcohol and tobacco in the United States. Use of these substances often begins during adolescence, however, including during the preteen years. The strongest predictor of drug use by youth is having friends who regularly use drugs, that is, alcohol, tobacco, or other substances (eg, marijuana). Additionally, it has been shown that the more risk factors identified, the greater the risk of substance use/abuse in the teenager.

Several factors are important precursors to (ie, risk factors for) drug use during adolescence. These risk factors include association with drug-using peers; attitudinal factors, such as favorable attitudes toward drug use in the family; low religiosity; poor school performance or academic failure, often beginning in the late elementary years; young age of initiation of alcohol or drug use; presence of a conduct disorder; environmental factors, such as the prevalence of drug use in a given community; history of child abuse; family history of alcoholism or drug use; poor parenting practices; high levels of conflict within the family; minimal bonding between parents and children; family disruption; and early and persistent problem behaviors during childhood, such as untreated attention-deficit/hyperactivity disorder (ADHD).

It is well documented in the literature that early age of onset of alcohol and tobacco use is predictive for the use of other drugs, a greater variety of drugs, and more potent agents. Additionally, the use of alcohol at an early age is associated with future alcohol-related problems, such as lifetime alcohol dependence and use/abuse. The early initiation of alcohol also results in increased sexual risk-taking behavior during adolescence (ie, unprotected sexual intercourse, exposure to multiple sexual partners, being drunk or high during sexual intercourse, increased risk of pregnancy) as well as academic problems and delinquent behavior later in adolescence. Long-term effects during young adulthood include difficulties with employment, criminal and aggressive behavior, and continued substance use/abuse. Potential long-term health risks associated with the early initiation of alcohol, tobacco, and substance use/abuse depend on the specific exposure but include conditions such as pulmonary disease, chronic liver disease, cardiovascular complications, and cancer.

The role of the media and technology in adolescent alcohol and tobacco use has been the subject of much discussion in the past 20 years. Previous studies confirmed that exposure to smoking on television and in movies was 1 of the key factors that prompted teenagers to smoke and that preteens whose parents forbad them from viewing R-rated movies were less likely to begin smoking or drinking. One prospective study reported that exposure to R-rated movies or having a television in the bedroom significantly increased the risk of initiating smoking for white teenagers. Additionally, watching more movie depictions of alcohol use is strongly predictive of drinking onset and binge drinking in adolescents in the United States. Advertising also contributes to the depiction of alcohol and tobacco use as normative activities. In fact, it has been reported that advertising may be responsible for up to 30% of alcohol and tobacco use among adolescents. The influence of advertising on adolescents is now even more apparent with the current marketing of electronic vapor products to attract teenage consumption.

Clinical Presentation

Adolescents who are consuming alcohol or are involved in drug use may present to the health professional in several different ways. Illicit substance use might be uncovered during a routine confidential interview at an annual health maintenance visit, preparticipation sports physical evaluation, or urgent care appointment. Alternatively, the adolescent might have physical symptoms including chronic cough, persistent allergies, chest pain, and fatigue. Chronic conditions, such as asthma, may continue to worsen despite appropriate therapy in the adolescent smoking tobacco or marijuana or using e-cigarettes.

Abdominal tenderness may be noted on physical examination and found to be associated with gastritis, hepatitis, or pancreatitis. The adolescent also may have been in a recent motor vehicle crash or involved in other trauma, or their parent or parents may report that their teenager exhibits frequent mood swings, irritability, or erratic sleep patterns.

Pathophysiology

Although several theories have been proposed to explain why casual substance use develops into use/abuse and addiction in some adolescents and young adults and not others, the most critical factor seems to be the presence of underlying psychopathology. Adolescents who have untreated major depressive disorders, ADHD, or schizophrenia, for example, may use mood-altering substances to manage unpleasant feelings of dysphoria and low self-esteem. Initially used as a

temporary measure, this method of self-medication increases the likelihood of chronic substance use/abuse.

It is well known that genetic influences also play a major role in adult use/abuse of alcohol; however, less evidence exists for adolescent drug use. What is known is that families and parental attitudes play a significant role in the development of alcohol and other drug use in teenagers. Permissive attitudes toward alcohol and drug use by parents or guardians and parental or older sibling drug use in the setting of other environmental risk factors are predictive of increased drug and alcohol use in the adolescent.

Differential Diagnosis

The differential diagnosis for symptoms and behaviors associated with substance use/abuse includes underlying psychiatric disorders. Affective, antisocial, and conduct disorders as well as ADHD can be the primary or secondary condition in adolescents who are abusing drugs. Like adults, adolescents may use illicit drugs to self-medicate associated depression, anxiety, or auditory hallucinations. The pharmacology and toxicity of the illicit substances most commonly used by adolescents are summarized in Table 63.1.

Evaluation

History

The interview should be conducted in a private, quiet area to minimize interruptions. If parents or guardians have accompanied the adolescent, they should be politely asked to leave the room after they have had an opportunity to express their concerns and after issues of confidentiality are addressed in the presence of both parties. Doing so helps avoid future uncomfortable moments when a parent or guardian returns and asks what was disclosed in their absence. After parents or guardians have left the room, issues addressing confidentiality and privacy should be reviewed once again with the patient. Special circumstances, such as a disclosure of sexual or physical abuse or possible suicidal ideation or homicidal intent, that dictate that confidentiality be broken also should be discussed with the teenager before proceeding with the interview (see Chapter 4).

The interview should proceed in a casual, non-pressured, nonjudgmental fashion. Initial inquiries should address less threatening general topics, such as school, home life, and outside activities, including activities with friends. Use of the HEADSS (home, employment and education, activities, drugs, sexuality [including a history of sexual abuse or assault], suicide and/or depression) assessment allows for a thorough review of the essential components of the psychosocial history (see Chapter 4). Another interview tool, the SSHADESS (strengths, school, home, activities, drugs and alcohol, substance use, emotions and depression, sexuality, safety) assessment, has been developed to emphasize and review positive components in an adolescent's life in addition to any high-risk behavior.

Some practitioners prefer to use questionnaires or other formal validated screening tools to initially obtain this background information. A questionnaire is given to patients to fill out while they are waiting to be seen, and responses are reviewed privately with the health professional during the actual visit. Some questionnaires address only issues concerning substance use/abuse, whereas others are more general but also include questions about alcohol, tobacco, and drugs (Figure 63.1 and Box 63.1). Controversy exists about the role of such questionnaires, primarily concerning the truthfulness of answers, because parents or guardians may be with teenagers as they are attempting to complete the form. Administering questionnaires via technology and in a designated, private space can help improve honesty.

More specific questions about the use of alcohol and tobacco as well as illicit substances should be asked after general subjects have been discussed (Box 63.2). If adolescents seem wary of answering these questions, it may be helpful to initially inquire about their friends. Questions should be phrased with the assumption that the responses will be affirmative (eg, "How many beers do your friends drink in a week? And do you drink the same amount?"). It is hoped that this less-threatening approach invites more honest answers. An assessment of the risk of suicidal behavior is also indicated.

Because many physicians lack unlimited time to interview adolescents and obtain all the details in a single visit, various standardized methods have been developed to efficiently screen teenagers for substance use in the context of health supervision visits. Brief screening tools that are both self- and interviewer-administered can be used to glean important information even in a busy practice. For example, 1 screening tool uses the following 3 questions: During the past 12 months, have you smoked marijuana? Have you drunk any alcohol? Have you used anything else to get high? If an adolescent answers "no" to all 3 questions, the patient should still be asked if he or she have ridden in a car with a driver who was high or had been using alcohol or drugs. Additional screening is recommended for any teenager who answers "yes" to any of the 3 initial screening questions. Six questions, known as the CRAFFT screening tool, are then reviewed with the adolescent to further identify drug and alcohol risk or problems associated with their use. The teenager receives 1 point for each "yes" answer; a total score of 2 or more indicates a positive result and high risk for a substance use disorder. It also indicates the need for additional follow-up as well as referral to a mental health professional or therapeutic treatment program. The validity of this brief, developmentally appropriate tool for screening adolescents has been reported in the literature and is well supported by experts in the field of adolescent and addiction medicine for use by primary care physicians. Another screening tool, funded by the National Institute on Drug Abuse, is the Screening to Brief Intervention tool (S2BI). It is used to assess the frequency of past-year substance use for tobacco, alcohol, marijuana, and 5 other classes of substances (Figure 63.1). Depending on the results of the S2BI tool, motivational intervention is recommended as the next step.

Physical Examination

Positive findings on physical examination are rare, especially in adolescents who consume alcohol or other substances only occasionally. In adolescents with a history of chronic substance use/abuse, however, certain physical findings may be present.

Table 63.1. Pharmacology and Toxicity of Substances Commonly Used by Adolescents

Substance	*Pharmacology*	*Effects*	*Toxicity*
Nicotine	Potent psychoactive drug that acts on receptors in the CNS to produce effects	Stimulation, relaxation, focused attention	Nontolerant individuals: weakness, nausea, vomiting, feeling unwell
Marijuana	Active ingredient (ie, delta-9-tetrahydrocannabinol) is rapidly absorbed into the bloodstream from inhaled smoke	Low dose: euphoria, relaxation, time distortion, auditory and visual enhancement High dose/toxic: mood fluctuations, hallucinations, paranoia, psychosis	Acute: panic attacks, psychosis (rare) Chronic: short-term memory impairment, amotivational syndrome, reduced sperm counts
Alcohol	Causes nerve cell membranes to expand and become more "fluid," thereby interfering with neuronal conduction Interference of neurotransmitters	Mild: disinhibition, euphoria, mild impaired coordination, mild sedation Moderate: increased sedation, slurred speech, ataxia	Severe: confusion, stupor, coma, respiratory depression
Cocaine	Increased release and decreased reuptake of biogenic amines causing CNS and peripheral nervous system stimulation Local anesthesia Vasoconstriction	Produces a sense of well-being and heightened awareness, decreased social inhibition, and intense euphoria	Delirium, confusion, paranoia, hypertension, tachycardia, hyperpyrexia, mydriasis
Stimulants (eg, amphetamines, crystal methamphetamine, ecstasy)	CNS stimulation (ie, sympathomimetic)	Heightened awareness; restlessness and agitation, decreased appetite Low doses increase ability to concentrate	Hypertension, hyperthermia, seizure, stroke, coma, arrhythmia
Hallucinogens (eg, LSD, mescaline, mushrooms)	Inhibits release of serotonin	Distortions of reality—perceptual alterations, synesthesia common (eg, "hearing" smells)	Paranoia, flashbacks, psychosis, depression
PCP	Dissociative anesthetic with analgesic, stimulant, depressant, and hallucinogenic properties	Dissociative anesthetic Dose-dependent euphoria, dysphoria, perceptual distortion	Psychoses; aggressive, violent behavior; depression; seizure, rhabdomyolysis
Opiates (eg, opium, heroin, methadone hydrochloride)	Binds to opioid receptors in CNS, causing CNS depression	Sedative analgesics Euphoria followed by sedation, somnolence	Respiratory depression, CNS depression, miosis, bradycardia, hypotension, arrhythmia, seizure, rhabdomyolysis
Sedatives (eg, benzodiazepines, barbiturates)	CNS depression, binds to specific receptor that potentiates GABA	Sedation, anxiety reduction	Similar to opioid intoxication
Anabolic steroids	Bind to androgen receptors at the cellular level, stimulate production of RNA and protein synthesis	Euphoria; increased irritability and aggressiveness; at high doses, induction of mental changes	Psychosis
Inhalants	CNS stimulation and excitement, progressing to depression	Euphoria, hallucinations, psychosis	Respiratory depression, arrhythmia, seizure, sudden sniffing death syndrome (ie, sudden death secondary to arrhythmia)

Abbreviations: CNS, central nervous system; GABA, γ-aminobutyric acid; LSD, lysergic acid diethylamide; PCP, phencyclidine hydrochloride.

Derived from Schwartz B, Alderman EM. Substances of abuse. *Pediatrics in Review.* 1997;18(6):204–215, and Joffe A, Blythe MJ, eds. Mental health, psychotropic medications, and substance abuse. *Adolesc Med.* 2003;14:455–466.

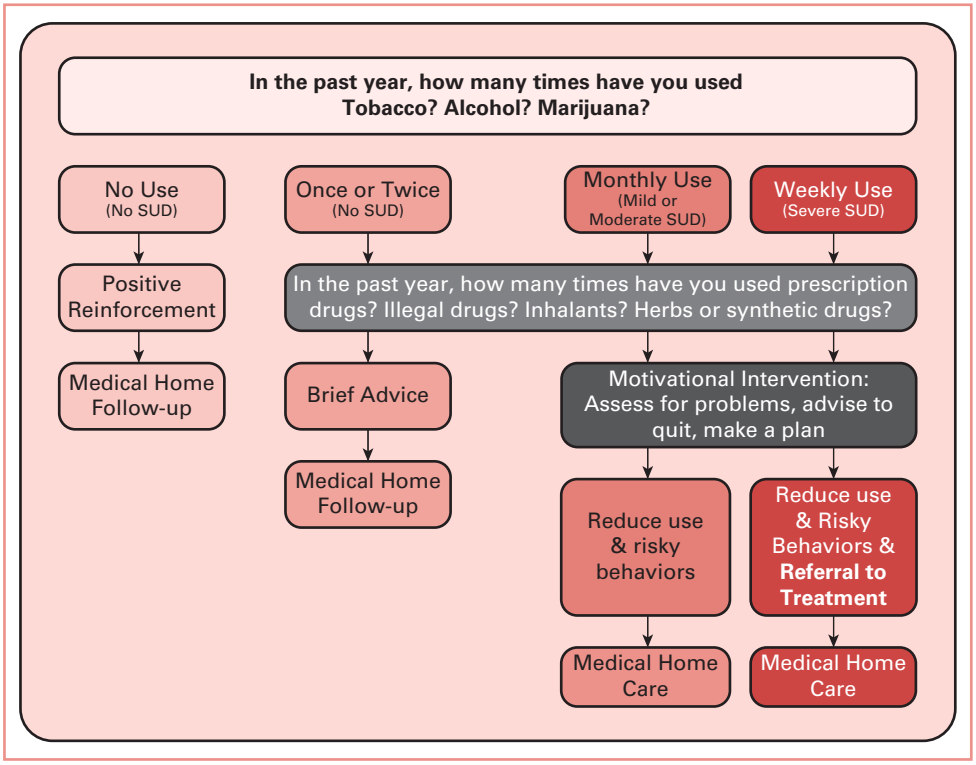

Figure 63.1. The Screening to Brief Intervention tool approach to clinical screening, brief intervention, and referral to treatment.

Abbreviation: SUD, substance use disorder.

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All vital signs should be reviewed. Tachycardia and hypertension occur primarily with acute intoxication with cocaine or stimulants (eg, amphetamines). The current weight also should be recorded and compared with previous values, and any significant weight loss should be noted. The skin should be examined closely for track marks, skin abscesses, or cellulitis, especially if the patient admits to using drugs intravenously. The skin should also be examined for evidence of self-injurious behaviors, such as cutting. Findings consistent with hepatitis (ie, hepatomegaly, jaundice) may be present in these individuals. The presence of diffuse adenopathy, thrush, leukoplakia, seborrheic dermatitis, or parotitis should raise the suspicion of HIV infection. A nonspecific maculopapular rash also may be seen during the acute viremic phase of an HIV infection. Upper respiratory symptoms, such as chronic nasal congestion, long-lasting "colds" and "allergies," and epistaxis can occur with chronic inhalation of cocaine or another illicit substance. Signs of nasal congestion, septal perforation, and wheezing also may be noted on examination. Additionally, smoking crack cocaine can cause chronic cough, hemoptysis, and chest pain. Smoking marijuana over long periods can result in similar findings. Gynecomastia can occur with use of anabolic steroids, marijuana, amphetamines, and heroin. The adolescent female using anabolic steroids may exhibit signs of virilization, such as a deep voice, hirsutism, and male pattern baldness. The detailed neurologic evaluation is arguably the most important aspect of the examination. Any abnormalities in memory, cognitive functioning, or affect should be noted. Chronic marijuana use is sometimes accompanied by amotivational syndrome.

Acute intoxication with some drugs (eg, cocaine) may result in delirium, confusion, paranoia, seizures, hypertension, tachycardia, arrhythmias, mydriasis, and hyperpyrexia. Acute PCP intoxication produces abnormal neurologic signs, tachycardia, and hypertension. Findings such as central nervous system and respiratory depression, miosis, and cardiovascular effects (eg, pulmonary edema, orthostatic hypotension) are consistent with opiate overdose. Signs and symptoms of acute intoxication generally are seen in the emergency department setting rather than in the primary care physician's office or clinic.

Laboratory Tests

In the clinic setting, routine drug screening as part of the initial evaluation of substance use is not recommended and generally not indicated to initiate treatment. Specific laboratory studies should be performed, however, in those patients with a history of known substance use/abuse and who are enrolled in a drug treatment program to monitor for abstinence; in patients who are required by court order; and in patients who exhibit acute altered mental status, intoxication, or abnormal neurologic findings, such as may be seen in an emergency department setting. In the office setting, these symptoms are frequently absent, and urine or serum studies to "check" for drug use are not particularly useful.

Box 63.1. Rapid Assessment for Adolescent Preventive Services

1. In the past 3 months, have you taken diet pills or laxatives, made yourself vomit (throw up) after eating, or starving yourself to lose weight?
2. Do you eat some fruits and vegetables every day?
3. Are you active after school or on weekends (walking, running, dancing, swimming, biking, playing sports) for at least 1 hour, on at least 3 or more days each week?
4. When you are driving or riding in a car, truck, or van do you always wear a lap/seat belt?
5. Do you always wear a helmet when you do any of these activities: ride a bike, rollerblade, or skateboard; ride a motorcycle, snowmobile or ATV; ski or snowboard?
6. During the past month, have you been threatened, teased, or hurt by someone (on the internet, by text, or in person) causing you to feel sad, unsafe, or afraid?
7. Has an adult ever physically injured you (by hitting, slapping, kicking) or has anyone ever forced you to have sex or be involved in sexual activities when you didn't want to?
8. Do you carry a weapon (gun, knife, club, other) to protect yourself from another person?
9. In the past 3 months, have you used any form of nicotine including vaping (e-cigarettes, Juul, RUBI, Suorin, Blu, hookah, vape pens), smoking (cigarettes, cigars, black and mild) or chewing tobacco (dip, chew, snus)?
10. In the past 12 months, have you driven a car while texting, drunk or high, or ridden in a car with a driver who was?
11. In the past 3 months, have you drunk more than a few sips of alcohol (beer, wine coolers, liquor, other)?
12. In the past 3 months, have you used marijuana (weed, pot, cannabis, THC) in any form such as vaping, smoking, edibles, drinks, pills, oil, or any other type?
13. In the past 3 months, have you taken a prescription medication (codeine, OxyContin, Norco, Vicodin, Adderall, Ritalin, Xanax, other) without a prescription, taken more than the prescribed amount or continued to take it after you no longer needed it?
14. Have you ever had any type of sex (vaginal, anal, or oral sex)?
15. Are you physically attracted to people who are the same gender as you (girl if you are a girl/guy if you are a guy) or do you feel that you are gay, lesbian or bisexual?
16. If you have had sex, do you always use a condom and/or another method of birth control to prevent sexually transmitted infections and pregnancy?
17. During the past month, did you often feel sad or down as though you had nothing to look forward to?
18. Do you have any serious problems or worries at home or at school?
19. In the past 12 months, have you seriously thought about killing yourself, tried to kill yourself, or have you purposely cut, burned, or otherwise hurt yourself?
20. Do you have at least one adult in your life that you can talk to about any problems or worries?
21. Do you destroy things, hurt yourself, or hurt other people when you are angry?

Box 63.2. What to Ask

Adolescent Substance Use/Abuse

- Do any of your friends drink alcohol, smoke marijuana or tobacco, or use any other drugs?
- What drugs, including alcohol and tobacco, are you currently using? For how long and how frequently?
- In what environments do you use these substances?
- Have you ever blacked out or been arrested while under the influence of drugs or alcohol?
- Has drug or alcohol use ever interfered with school, work, or other social activities?
- Has drug or alcohol use adversely affected relationships with family, friends, or romantic partners?
- Have you ever had sexual encounters while under the influence of drugs or alcohol?
- Do you ever use drugs or alcohol to feel better or to forget why you feel sad?
- Do your parent(s) or guardian(s) use alcohol, tobacco, or illicit drugs?
- Is there a f amily history of alcoholism, addiction, or mental health issues?

If these tests are performed in an ambulatory setting and the patient is awake and alert, the adolescent's consent is recommended despite adamant requests from a parent or guardian. The results should not be shared with anyone other than the patient, unless the patient gives permission or the test was ordered while investigating the cause of an acute medical condition. According to the American Academy of Pediatrics and the Society for Adolescent Health and Medicine, obtaining a urine drug test without the consent of the adolescent undermines the physician-patient relationship and the development of a meaningful, trusting relationship at this critical time in the patient's life. Drug testing should not be performed simply to allay parental anxiety or confirm suspicions about possible substance use/abuse for a parent, teacher, or athletic coach unless previously authorized by the adolescent.

If urine is obtained for drug testing, it is critical that the sample be collected in a controlled manner and not contaminated, diluted, or altered in any way. The physician should also be familiar with the particular laboratory performing the drug test as well as the reported sensitivity and specificity of each test. Urine testing is available to detect marijuana and its metabolites, cocaine, amphetamines, PCP, opiates, barbiturates, and benzodiazepines. Blood levels can be obtained for alcohol, marijuana, cocaine, amphetamines, barbiturates, and benzodiazepines. Although salivary or urinary concentrations of cotinine and nicotine concentrations can also be performed, these measurements are used mainly in research studies.

Testing for specific inhalants is not routinely done. The deleterious effects of these substances on the hematologic, hepatic, and renal systems can be evaluated by performing a complete blood count, liver function tests, prothrombin time and partial thromboplastin time, and blood urea nitrogen and creatinine; however,

results are generally nonspecific. Testing for synthetic cannabinoids, dextromethorphan, and 3,4-methylenedioxymethamphetamine (ie, ecstasy) is not typically included in drug panels.

Management

The clinical approach to the management of substance use in the adolescent is dependent on the patient's degree of risk-taking behavior and drug involvement (ie, experimentation, limited use, problematic use, abuse, or addiction/dependence); the physician's relationship with the adolescent and family; the adolescent's desire to change his or her their behavior; and the family's involvement and awareness of the extent of the problem. A more detailed discussion is found in the 2016 policy statement, "Substance Use Screening, Brief Intervention, and Referral to Treatment," by the American Academy of Pediatrics Committee on Substance Use and Prevention.

Anticipatory Guidance

If preteens (ie, middle school students) or adolescents and their peers are not participating in any high-risk behaviors, including tobacco, alcohol, or drug use (ie, the answers to all 3 CRAFFT screening questions are "no"), pediatricians should provide patients with both positive reinforcement for their abstinent behavior and age-appropriate anticipatory guidance. This should include advice and information on safety issues; consequences of alcohol and tobacco use, including use of e-cigarettes; and exposures to peers who may be using illicit and prescription drugs. Adolescents should be praised for making smart choices and encouraged to continue their current behavior but should be invited to return to the office if they have any questions or concerns. This may be particularly helpful for patients whose daily environment exposes them to high-risk situations for alcohol and drug use. The pediatrician should encourage an open dialogue about substance use/abuse between adolescents and their parents or guardians to assist teenagers in developing strategies for drug avoidance.

Early Intervention

Primary care physicians should provide early intervention guidance to preteens and adolescents who have begun or are engaging in occasional high-risk behavior and are considered to be at moderate risk for substance use–associated problems. These are patients who have started using alcohol or drugs and score 0 or 1 on CRAFFT screening. Such use implies only occasional or casual use of illicit substances by patients or peers. This scenario is the most challenging because many adolescents, as well as their parents or guardians, perceive occasional alcohol or drug use as "experimental" or a phase of "normal teenage behavior" and therefore may trivialize any advice given by the pediatrician. Interventional guidance involves clear advice to stop alcohol and other drug use and a discussion of potential risks created by the adolescent's current behavior. For example, individuals who drink alcohol or smoke marijuana at parties are at increased risk for involvement in a motor vehicle crash afterward as the driver or passenger. Another common scenario involves alcohol intoxication and poor judgment about sexual behavior. All teenagers should be made aware of the possible consequences of their unsafe behavior, especially if their occasional drug use has progressed to more regular use in risky situations. Furthermore, they should receive educational counseling about the unhealthy effects of alcohol use in adolescence (eg, the deleterious effects of alcohol on developing brain cells). Experts also recommend including strength-based counseling to recognize the positive qualities of the adolescent.

Specialized Programs

Preteens or adolescents who are routinely using drugs, alcohol, or tobacco but are clearly motivated to stop often can be treated solely by their primary care physician or collaboratively with child and adolescent mental health specialists. Teenagers who began using illicit substances at an older age, have a fairly good relationship with their families, have supportive relationships with friends who do not use drugs, and who continue to do well in school and participate in other outside activities are more likely to be successful than teenagers who start at a younger age. The physician initially should identify the problem and establish whether the adolescent desires to change his, her, or their behavior. After obtaining the patient's consent, the physician should meet with the family, develop an appropriate strategy for treatment intervention, and follow the adolescent periodically in the office. Timely and consistent reinforcement by the primary care physician is necessary, especially in the beginning of treatment. Referral to an outpatient program, such as Alcoholics Anonymous, Alateen, or Narcotics Anonymous, also may be indicated. Appropriate community resources for the teenager and family should be reviewed. Continued coordination of services by the pediatrician is challenging but essential to ensure adherence by the adolescent and cooperation by the family to maximize the adolescent's chance for a full recovery.

Mental Health or Treatment Programs

Referral to a mental health or addiction specialist or a specialized treatment program (eg, drug detoxification center) is indicated for the adolescent who displays clear signs of dangerous behavior and continues to use drugs despite office treatment by the primary care physician and adverse effects on the adolescent's daily life and relationships. Immediate intervention is also necessary for the adolescent who is using intravenous drugs, combining sedative drugs, or consuming large quantities of alcohol. Additionally, the teenager with a suspected concomitant psychiatric condition should be referred immediately for psychiatric evaluation. Other criteria for specialty treatment programs include a chronic history of substance use/abuse, a serious life-threatening event in conjunction with substance use/abuse (eg, attempted suicide, motor vehicle crash), familial strife, or persistent involvement with a drug-dependent crowd. Primary care physicians should become familiar with local inpatient programs and residential treatment facilities in their community and partner with mental health and addiction specialists to provide the patient and family with optimal services. Although the selection of a program may be influenced by financial resources and insurance coverage options, it is quite important to try to select the most appropriate program for the individual adolescent and family. Guidelines

exist to aid the physician in the selection process for public and private facilities. These guidelines include total abstinence, appropriate professionals with expertise in drug addiction, familial involvement in the program, family therapy, and appropriate outpatient follow-up. Regardless of the final course of action of the patient, it is important for the primary care physician to remain involved with the family while making these difficult decisions and support their experience throughout the recovery process.

Prevention Programs

Prevention programs have been developed to assist young people from preteens to young adults and influence their decisions about the use of alcohol, tobacco, and other illicit substances. Current programs focus on multiple aspects of the lives of children and adolescents. Programs may involve individual decision-making, self-esteem, and basic education about alcohol, tobacco, and drugs. These programs frequently emphasize positive communication skills, strong family values and dynamics, influential parenting skills, and positive peer associations. Structured curricula also have been created for use in the schools, and community outreach programs have been organized by groups such as local police departments. The effectiveness of each type of program is a subject of controversy, but each is aimed at preventing the initial or continued use of illicit substances among children, preteens, and adolescents. *Reaching Teens: Strength-Based, Trauma-Sensitive, Resilience-Building Communication Strategies Rooted in Positive Youth Development,* is an excellent resource and guide for parents and health professionals.

Prognosis

It is difficult to assess the exact outcome for the adolescent who undergoes treatment for substance use/abuse, because definitions of success vary. For some teenagers, success implies periods of sobriety; for others, it means complete abstinence; and for still others, it is abstinence in addition to recovery from other contributing psychological problems. Specific outcomes data indicate that abstinence rates are positively correlated with regular attendance in a support group and parental participation in these groups. Additionally, general success rates range from 15% to 45%, depending whether the tool assesses short- or long-term outcomes. A lifetime potential exists for relapse among all adolescents with a history of substance use/abuse.

CASE RESOLUTION

The adolescent is at high risk for continued substance use/abuse because of his association with friends who use drugs as well as his own ongoing tobacco use, possible school failure, and recent change in extracurricular activities (ie, dropping out of baseball). The physical examination findings also are consistent with his smoking history. The physician should review these risk factors with the teenager in private and acknowledge the difficulty in removing oneself from such an environment. The adolescent's motivation to change his behavior should be assessed, and referrals to special intervention programs can be discussed. Regardless of the outcome, the physician should continue to see the teenager at an agreed-on interval to monitor his ability to quit smoking and change his high-risk behavior.

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CHAPTER 64

Eating Disorders

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CASE STUDY

A 16-year-old girl is brought to the office by her mother because the mother feels that her daughter is too thin and always appears tired. The mother reports that her daughter does not eat much at dinner and generally says she is not hungry. Recently, the girl bought diet pills that were advertised online. The teenager claims that she has not taken the pills, so she does not understand why her mother is so upset. She says she feels fine and considers herself healthy because she has recently become a vegetarian.

The girl is a 10th-grade student at a local public school and attends classes regularly, although her friends are occasionally truant. She is involved in the drill team, swim team, and student council. She has many friends who have "nicer" figures than she does. Neither she nor her friends smoke tobacco or use drugs, but they occasionally drink alcohol at parties. The girl is not sexually active and denies a history of abuse. Her menstrual periods are irregular, with the last occurring approximately 3 months prior to this office visit.

She currently lives with her mother, father, and 2 younger siblings. Although things are "OK" at home, she thinks her parents are too strict and do not trust her. They have just begun to allow her to date, but she dislikes that she has a curfew.

The physical examination is significant for a thin physique, and vital signs are normal. On the growth chart, her weight is at the 15th percentile and her height is at the 75th percentile; her body mass index is 17 (10th percentile). Her weight at a previous visit was at the 40th percentile. The remainder of the physical examination is unremarkable.

Questions

1. What are the common characteristics of disordered eating in adolescents?
2. What are the important historical points to include when interviewing the patient with suspected eating disorder? Which teenagers are considered at risk?
3. How is the diagnosis of anorexia nervosa and bulimia nervosa made?
4. What is the treatment plan for the adolescent with eating disorder?
5. What are the medical complications of anorexia nervosa and bulimia nervosa?
6. What is the prognosis for these conditions? How can the primary care physician help improve the outcome?

Basic characteristics of eating disorders are summarized in Box 64.1. For more stringent criteria, refer to *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria. An adolescent may have an atypical presentation, a history of anorexia nervosa (AN) and bulimia nervosa (BN), or an underlying affective component that confuses the issue. The adolescent may not display a blatant refusal to eat but may instead exhibit subtle characteristics of disordered eating, such as constant dieting, obsession with a certain physical exercise, or irregular menstruation. Additionally, preoccupation with physical appearance and weight currently is not uncommon or necessarily pathologic in Western society. The fashion industry and social media promote the idea that thinness and beauty are interrelated. Thus, the typical adolescent who longs to be accepted by peers and who is learning to develop a sense of independence and control is a prime target for the development of disordered eating. The primary care physician is in a unique position to recognize individuals at risk, appropriately screen teenagers with specific behaviors, and provide early diagnosis of and intervention for patients with disordered eating to prevent the development of potentially lethal complications associated with these conditions. The overall goal is to decrease the lifelong medical and psychological morbidity and mortality associated with AN and BN to enhance the long-term health and emotional well-being of affected individuals.

Epidemiology

Historically, eating disorders predominately affected white adolescent females in more affluent communities. Although disordered eating currently occurs in many other settings, historically, AN and BN were rare among persons of lower socioeconomic status, among ethnic/racial minorities, and in children younger than 12 years of age. Currently, these conditions are diagnosed in individuals of all ethnic, cultural, and socioeconomic backgrounds in the United States as well as in other developed countries. Additionally, males make up an estimated 5% to 10% of all patients with eating disorders and tend to be younger, malnourished, or medically unstable when they present for treatment, which is suggestive of delayed evaluation and diagnosis.

Although dieting behavior among adolescents and young adults is not uncommon, true AN has a prevalence of approximately 0.5%

Box 64.1. Criteria for Anorexia Nervosa and Bulimia Nervosa

Anorexia Nervosa

- Caloric intake below caloric requirements (low weight for age, sex, developmental stage, physical well-being)
- Fear of weight gain or becoming overweight/obese
- Distorted body image
- Failure to recognize dangers of low weight
- Types:
  - *Restricting type:* Characterized by dieting, fasting, and/or excessive exercise.
  - *Binge-eating/purging type:* Characterized by binge eating associated with self-induced vomiting or the misuse of diuretics, laxatives, suppositories, or enemas.

Bulimia Nervosa

- Binge eating
- Eating larger than normal amounts of food
- A sense of being out of control and using other behaviors to restrict weight gain (eg, excessive exercise, fasting, vomiting, laxatives, diuretics, or other medications)

Derived from *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.

to 1% in these individuals. Estimates have ranged from 1% to 10% in high-risk groups, such as upper- and middle-class white females. Less than 5% of these cases are males, with a female-to-male ratio of 9:1, although this prevalence has been disputed to be an underestimate of young males with AN. The age of onset historically was reported to occur during middle adolescence (age 14–16 years). It has become increasingly more common, however, for school-age children and younger teenagers to be dissatisfied with their weight and concerned with body image. Studies of middle-income elementary school girls have reported significant body and weight dissatisfaction. Skipping meals and desserts, fasting, and vomiting all have been reported specifically to lose weight. For many of these young girls, the goal is not to maintain a normal weight but to be underweight by standard growth charts.

The prevalence of BN is approximately 1% to 4%, although some studies report that as many as 8% of adolescent and college women and 0.5% of men have bulimia. The age of onset of BN tends to be later than for AN, with symptoms beginning during late adolescence and young adulthood (age 17–20 years). Several behavioral and affective disorders have been associated with the development of AN and BN. These include comorbid psychiatric conditions, such as depressive, bipolar, and anxiety disorders; alcoholism and substance use; other addictive behaviors (eg, laxative abuse); poor impulse control; and obsessive-compulsive personality. Girls who are obese or experience early puberty also are at increased risk for developing an eating disorder, with symptoms starting in the context of dieting. A history of sexual abuse may be present among patients with eating disorders. Additionally, suicidal behavior (ie, attempts) is more likely in individuals with BN, as are reports of an increased incidence of family members with substance use and dependence disorders. Generally, eating disorders occur with increased frequency in patients with a family history of eating and mood disorders as well as obesity.

Variants of eating disorders, which do not meet full diagnostic criteria based on previous guidelines but cause significant distress and impairment in social, occupational, or other important areas of functioning, are not uncommon in preteens and adolescents. Exact numbers are uncertain because many of these patients remain "under the radar" and the consequences of their eating behaviors are not fully recognized. Additionally, more than one-half of junior high and high school girls have dieted at some time, many of them repeatedly. For this reason, the revised *DSM-5* criteria for both AN and BN are less restrictive. New diagnostic categories now include the spectrum of patient behaviors: avoidant/restrictive food intake disorder, atypical AN, and binge-eating disorder.

Clinical Presentation

The patient with eating disorder may present with general symptoms related to weight loss and nutritional or volume deficiencies, such as fatigue or syncope. Such a patient also may exhibit minimal weight gain according to standard growth charts or a delay in the onset of puberty or progression of pubertal development. More importantly, female adolescents also may present with primary or secondary amenorrhea noted incidentally during an annual health maintenance or sports physical examination. Sometimes an underlying psychiatric condition, such as obsessive-compulsive disorder or anxiety, is the impetus for the medical referral. Occasionally, a patient with undiagnosed eating disorder is hospitalized because of complications related to the condition, such as electrolyte disturbances associated with diuretic use, hematemesis from induced vomiting, or syncope from hypovolemia. Finally, the preteen or adolescent may be referred to the primary care physician by a concerned parent, well-intentioned friend, informed coach, or astute school personnel who notice significant weight loss or restrictive eating patterns.

Pathophysiology

Anorexia Nervosa

Although several risk factors predispose an individual to the development of AN, this condition, like other eating disorders, has no single cause (Box 64.2). Longitudinal studies clearly point to a significant role for inappropriate dieting behavior in the pathogenesis of an eating disorder. Because not all dieters develop an eating disorder, however, other contributing risk factors must be involved. Current theory suggests that the etiology of AN is multifactorial and precipitated by a complex interaction between genetic, environmental/cultural, and psychological risk factors, along with the adolescent's personal experiences and individual personality traits.

Biologic Factors

It has been postulated that the normal increase in adipose tissue with the onset of puberty creates special challenges for some girls. An eating disorder may develop as an attempt to control or combat this

Box 64.2. Risk Factors for the Development of an Eating Disorder

- Family history of an eating disorder or obesity
- Affective illness or alcoholism in a first-degree relative
- Specific activities/sports: ballet, gymnastics, modeling, dance, figure skating, long-distance running, wrestling, lightweight rowing, pole vaulting
- Personality characteristics (eg, perfectionism)
- Parental eating behavior and weight
- Low self-esteem
- History of physical or sexual abuse
- Body image dissatisfaction
- History of excessive dieting, frequently skipped meals, compulsive exercise

Adapted from Rome ES, Ammerman S, Rosen DS, et al. Children and adolescents with eating disorders: the state of the art. *Pediatrics.* 2003;111(1):e98–e108.

normal pubertal weight gain with the initiation of dieting behavior. Preexisting hypothalamic dysfunction also has been implicated as a contributing factor to AN. Additionally, changes in neurotransmitter levels have been shown to occur with initial vomiting or dieting. These changes may result in specific psychiatric symptoms that may perpetuate disordered eating. Recent data obtained with neuroimaging studies have shown that most of the physiological disturbances resolve with normalization of the patient's body weight, however. Additionally, a premorbid disturbance in the neurotransmitter serotonin has been speculated to be a risk factor for the development of AN and BN. Serotonin controls appetite by creating a sensation of fullness or satiety. It is also known to affect sexual and social behavior, mood, and stress responses. Although further studies are needed to confirm the exact role of this hormone in the development of an eating disorder, it has been shown that decreases in this brain neurotransmitter have been associated with impulsivity, aggression, and depression.

Leptin, a circulating hormone produced in adipose tissue, also seems to have a significant role in mediating the neuroendocrine effects of AN. Decreased concentrations of leptin are seen with reduced body fat stores as a result of decreased caloric intake and energy deficits. Paradoxically, leptin levels also appear to contribute to physical hyperactivity (eg, compulsive exercise, restlessness), which is often seen in patients with AN despite their inadequate metabolic intake.

Genetic Factors

A genetic predisposition to anorexia has been shown in studies of monozygotic twins. The incidence of the disorder is increased in sisters and other female relatives of patients with AN.

Personal Characteristics

Generally, patients with AN are described as obsessive-compulsive personality types, perfectionists, and overachievers, particularly in academics and sports. They also display low self-esteem and high anxiety levels despite their perceived successes by others. In the case of girls, they are the "model daughters" who have never caused any previous problems because of their compliant, self-sacrificing, dutiful, nonassertive nature.

An increased association exists between AN and major depression, and many studies of women have shown that first-degree relatives of patients with AN have higher rates of depression than the general population. Many depressive symptoms in patients with AN improve with restoration of body weight, however. Therefore, some of these clinical features of depression also may be secondary to the adolescent's state of severe malnutrition or starvation.

Familial Influences

Researchers have noted that certain family dynamics may serve to initiate and perpetuate AN, although it is no longer believed that family dysfunction is the main cause of disordered eating. Typically, however, the family is overprotective and rigid, with the mother often enmeshed in her daughter's life. Conflict resolution tends to be poor, and an inability to express feelings within the family is often evident. Diagnosis of an eating disorder often causes additional stress in the family, thus contributing to more difficulties in their relationships. Multiple case-control studies have shown an increased rate of AN and BN in relatives of patients with eating disorders. This may be the result of inheritance patterns of personality traits as well as comorbid mood and anxiety disorders. Although there is limited research, studies suggest that there is no difference in familial or genetic factors between males and females with eating disorders.

Social/Environmental Pressures

The media as well as postindustrial, high-income societal standards are believed to play a role in setting the stage for the development of eating disorder. Individuals in affluent communities are especially at risk if thinness, food, eating, and obsessive exercise become the prime focus of daily activity. In addition, young women become caught in what has been labeled a "slender trap," in which thinness is equivalent to attractiveness and success. Food restriction or purging is a means of attaining thinness. An inability to maintain thinness equals failure. Role models in the media, such as fashion models and actors, also serve as ideals by which young people create their physical standards.

Other Influences

Involvement in particular extracurricular activities that promote leanness and endurance, such as ballet, gymnastics, figure skating, cheerleading, and running, may contribute to the development of AN in females. For male athletes, such influences include participation in sports such as wrestling, lightweight rowing, pole vaulting, and long-distance running, in which maintaining a low weight is important and dieting and/or fasting is used to achieve that weight limit. Chronic medical conditions, such as diabetes mellitus or inflammatory bowel disease (IBD), also may contribute to the development of an eating disorder.

Bulimia Nervosa

Several theories have been proposed to explain the etiology of BN but, similar to AN, no single etiology has been confirmed. Most likely, multiple factors contribute to the development of this eating

disorder, and it is the complex interaction between these factors at a particular developmental point in an older adolescent's life that results in this condition.

Biologic, psychological, familial, and societal influences are thought to contribute to the development of BN in older teenagers and young adults. Among other issues, adolescent and parental obesity are risk factors for BN, as are early menarche, early sexual experiences, posttraumatic stress disorder, and a history of childhood sexual or physical abuse that occurs in conjunction with a comorbid psychiatric condition. More important, dieting has been documented as an important risk factor in this age group.

Familial dysfunction and high levels of conflict also have been associated with BN. Unlike with AN, conflict might be discussed openly but negatively within the family, and the existence of inadequate expression of emotions may result in a lack of parental warmth and concern. As a result, the relationship between the parent and teenager is distant rather than enmeshed. The adolescent generally has a low level of self-esteem, high impulsivity, perfectionist temperament, and body image dissatisfaction. Additionally, parents and relatives have a high rate of affective and eating disorders as well as alcoholism.

Differential Diagnosis

It is important to differentiate AN from BN, although occasionally this distinction may be difficult to make if a patient displays behaviors consistent with both conditions. Additionally, approximately 50% to 60% of patients with eating disorders have associated comorbid psychiatric disorders. Major affective disorders to consider include depression, bipolar disorder, and obsessive-compulsive disorder. Anxiety disorders and substance use also are commonly seen, although the latter is more strongly associated with BN.

Weight loss, loss of appetite, and refusal to eat can be associated with many medical conditions. Therefore, other diagnoses to consider when evaluating patients for AN include IBD, malabsorption, celiac disease, diabetes mellitus, occult malignancies, AIDS, Addison disease, hyperthyroidism or hypothyroidism, hypopituitarism, tumors of the central nervous system, and chronic substance use, particularly with amphetamines and cocaine. Superior mesenteric artery syndrome is another important condition to consider in the differential diagnosis; however, it also can be a consequence of an eating disorder, specifically AN.

Evaluation

History

A complete medical history, including a detailed review of systems, should be obtained from all adolescents and young adults with suspected eating disorder to rule out the multiple other conditions in the differential diagnosis of decreased appetite and weight loss. The primary care physician then should interview the patient alone and focus on establishing the diagnosis of disordered eating by addressing more specific issues related to changes in food preferences (eg, vegetarian, vegan, low-fat diet), eating behaviors, dieting, calorie counting, weight history, exercise routine, and body image concerns (Box 64.3). The 2008 article titled "Interviewing the Adolescent With an Eating Disorder" includes a detailed discussion of interviewing techniques to use on patients with a suspected eating disorder. The severity of the medical and nutritional aspects of the condition should be determined, after which a thorough psychosocial

Box 64.3. What to Ask

Eating Disorders Generally

- Have there been any changes in the adolescent's weight? What is the most and least the adolescent has ever weighed? When did these weights occur and for how long?
- How does the adolescent feel about how they look? Is there anything they would like to change? How long have they been feeling this way?
- How much does the adolescent want to weigh or think they should weigh?
- How often does the adolescent weigh themselves?
- How much of the day is spent thinking about food?
- What is a typical day of eating like, including eating times, types of foods, beverages, amount consumed, and portion size? Do they have a mealtime ritual?
- What did they eat yesterday (24-hour dietary recall)?
- Does the adolescent have any food restrictions? Is the teenager a vegetarian? Do they count calories, fats, and carbohydrates? Binge eat?
- Does the adolescent hide or throw away food?
- Do they feel guilty about eating?
- How do the adolescent and the adolescent's friends manage weight control?
- What does the adolescent do when he, she, or they feels "fat"? Does the adolescent vomit to lose weight? How often does this occur? Are there particular triggers?
- Has the adolescent or any of the adolescent's friends ever used diuretics, diet pills, coffee, enemas, or laxatives to lose weight or compensate for overeating?
- Does the adolescent exercise? If so, what type and how often? Does the adolescent feel stressed if a workout is missed or delayed?
- In what sports or dance activities, if any, does the adolescent participate?
- For females, are menstrual periods regular? Last menstrual period? Age at menarche?
- Does the adolescent have any other symptoms associated with complications of eating disorders?
- Does the adolescent have any depressive symptoms, such as sleeping problems or fatigue that can accompany eating disorders?

For Patients with Bulimia Nervosa Specifically

- When do binges occur? With what foods?
- How much does the adolescent binge, and how often?
- What are the precipitating factors?
- What happens specifically during a typical episode?
- Does the adolescent vomit? How often?
- Does the adolescent use drugs or alcohol?
- Is there a history of depression or attempted suicide? Self-injurious behavior? Sexual or physical abuse?

evaluation should be conducted. Inquiries should focus on symptoms associated with complications of eating disorders, such as dysphagia secondary to esophagitis from recurrent vomiting, constipation from fluid restriction, and muscle weakness associated with emetine toxicity from chronic ipecac use. Because ipecac is no longer readily available, this adverse effect is seen less frequently than in the past. Although rarely seen by the primary care physician at the initial visit when the diagnosis of an eating disorder is made, recognition of serious medical complications is paramount to determining the type and urgency of further care.

Interviewing an adolescent with an eating disorder can be quite challenging; however, a thorough psychosocial assessment should be performed after a discussion about confidentiality has occurred with the adolescent and the parent. The HEADSS assessment (home, employment and education, activities, drugs, sexuality, suicide/depression) is useful to direct the psychosocial interview from general topics to more sensitive ones (see Chapter 4). Particular attention should be paid to the adolescent's overall functioning at home, with friends, and at school; the presence of other comorbid psychiatric disorders (eg, depression, anxiety); and a history of suicidal ideation or sexual and/or physical abuse. Out-of-control behavior as a result of substance use also should be assessed. The use of psychological testing or questionnaires to assess cognition, anxiety, and depression may be beneficial, depending on the comfort level of the primary care physician with these tools. Several validated screening tools specific for eating disorders also exist, including the Eating Disorders Examination Questionnaire (EDE-Q), Eating Disorder Inventory-3 (EDI-3), Eating Attitudes Test (EAT), and the Female Athlete Screening Tool (FAST). If the primary care physician is unfamiliar or uncomfortable with these tools, consultation with a mental health professional is warranted.

A detailed menstrual history also must be obtained from females because secondary amenorrhea is frequently an early sign of AN secondary to decreased body fat. Primary amenorrhea in the context of pubertal delay also can occur with AN. With BN, menses may be irregular or absent. A family history of eating disorders, substance use, or psychiatric disorders should be reviewed with the teenager and confirmed by the parent or guardian.

A dietary history should be obtained from the adolescent as well as the parent or guardian independently and should focus on any dietary restrictions or aversions. This may be difficult initially because the patient often does not believe he, she, or they has a problem with food. A 24-hour dietary recall can be an important place to begin the assessment. The presence of dieting or calorie counting, binge-eating and purging behaviors, amount of food consumed, and the frequency and duration of these behaviors should be documented by the physician or a registered dietician.

Physical Examination

In both AN and BN, the patient should undress, wearing only undergarments, for the physical examination. This prevents hiding the true body habitus with bulky clothes. The current height and weight should be plotted on a growth chart and the body mass index calculated (weight [kg]/height [m^2]). Delayed growth or short stature should be noted, because it can occur with severe malnutrition as well as other systemic conditions. Vital signs, including blood pressure, should be recorded and compared with previous measurements. Evidence of cardiovascular instability can be manifested by tachycardia, bradycardia, or orthostatic hypotension. The patient also may be hypothermic as a result of overall malnutrition. The general appearance and affect of the patient must be noted. The adolescent with typical AN is often emaciated, with an obvious loss of subcutaneous tissue, and may appear apathetic or anxious or have a flat affect. The patient with BN may have mild obesity or normal weight with a full-appearing facies secondary to parotid and submaxillary swelling, which is a complication of frequent purging. In most cases, however, the teenager appears "normal" at the initial visit.

Characteristic physical findings in patients with AN are consistent with a "state of hibernation," because the body adapts to starvation by slowing metabolism and decreasing energy requirements to a minimum. Hypothermia, orthostatic hypotension, bradycardia, and lanugo (ie, downy hair) on the arms and back are seen in patients with restrictive AN. The palms and soles may be yellow secondary to hypercarotenemia, and pigmentation of the chest and abdomen may be increased as a result of malnutrition. Thinning or loss of pubic and scalp hair as well as dry or pale skin also may be seen. The breasts should be examined carefully for sexual maturity rating (ie, Tanner stage) as well as galactorrhea. The presence of galactorrhea, along with a history of amenorrhea, warrants further investigation for a prolactinoma. The patient with AN may have interrupted or delayed pubertal development. A cardiac murmur must be noted and evaluated further, because one-third of patients with anorexia have mitral valve prolapse. The abdomen should be palpated for tenderness or masses and may be scaphoid in appearance. Bowel sounds are often decreased in the patient with anorexia, and stool may be palpated secondary to constipation. The presence of pubic hair (ie, genital sexual maturity rating) also should be noted. A rectal examination should be performed for the patient with a history of bloody stool, which is a finding consistent with IBD, or evidence of rectal prolapse. The extremities should be evaluated for coldness, mottling, or edema. They also should be palpated for tenderness because fractures may be present resulting from loss of bone mineralization. The skin, particularly the forearms, should be examined for any evidence of self-injurious behavior (eg, cutting). Finally, a complete neurologic examination, including a mental status evaluation and fundoscopic examination, should be performed to exclude a central nervous system lesion or endocrine disorder.

In the patient with BN, specific physical findings, if any, often are associated with dehydration and electrolyte imbalances that occur as a result of chronic vomiting or laxative abuse. Vital signs should be reviewed for tachycardia, sinus bradycardia, and orthostatic hypotension; the presence of any of these signs is indicative of hemodynamic instability. The patient also may have hypothermia. The skin should be inspected on the dorsum of the hand over the knuckles

for scratches, scars, or calluses from self-induced vomiting (Russell's sign). Periorbital petechiae and subconjunctival hemorrhages also may occur as a result of recurrent or severe retching. The oropharynx should be inspected for dental caries, enamel erosion, or discoloration as well as for parotid hypertrophy. Additionally, palatal scratches or mouth sores are evident. The abdomen should be palpated for epigastric tenderness, fullness, or midabdominal pain. Positive findings may be the result of esophagitis, gastritis, or pancreatitis.

Any muscle weakness or cramping should be appreciated and may be indicative of an electrolyte abnormality. Edema of the extremities may be noted in the patient who abuses laxatives.

Laboratory Tests

Box 64.4 lists the laboratory studies necessary in the evaluation of the patient with AN and evidence of malnutrition or purging behaviors. A complete blood cell count may be helpful because leukopenia, anemia, and, rarely, thrombocytopenia can occur with this disorder. Electrolytes (ie, sodium, potassium, chloride, carbon dioxide) and blood urea nitrogen are important, especially if the patient uses diuretics, laxatives, or ipecac. Serum magnesium, calcium, and phosphorous must be monitored, especially in the refeeding phase of treatment. The erythrocyte sedimentation rate may be low with anorexia and high with IBD or other inflammatory process. Normal liver function tests aid in excluding other causes of weight loss. Normal serum amylase and lipase levels rule out other etiologies for recurrent vomiting, such as pancreatitis. Serum tissue transglutaminase and immunoglobulin A levels can be obtained if concern exists for celiac disease. Other urine and serum tests (eg, thyroid function tests) help differentiate an endocrine disorder from AN, especially in the patient with primary or secondary amenorrhea (Box 64.5). Electrocardiography is used in diagnosis of QTc prolongation, heart block, and arrhythmias. Additionally, electrocardiography is indicated for the patient with electrolyte abnormalities or a history of significant purging or weight loss.

Laboratory abnormalities in BN reflect the type and extent of purging behavior of the adolescent with this diagnosis. Box 64.4 summarizes the necessary laboratory studies for the patient with BN.

Box 64.4. Initial Laboratory Assessment for the Patient With an Eating Disorder

Anorexia Nervosa

- Complete blood cell count, erythrocyte sedimentation rate
- Serum electrolytes (sodium, potassium, chloride, carbon dioxide)
- Blood urea nitrogen/creatinine
- Serum glucose
- Serum calcium, phosphorous, magnesium, zinc
- Serum protein, albumin, cholesterol
- Liver function tests
- Endocrine laboratory tests (perform in patients with amenorrhea)
  - Urine pregnancy
  - Follicle-stimulating hormone
  - Luteinizing hormone
  - Estradiol
  - Thyroid function: thyroid-stimulating hormone, thyroxine 4, thyroxine 3
  - Prolactin
- Urine pH and urinalysis
- Electrocardiography

Bulimia Nervosa

- Serum electrolytes (sodium, potassium, chloride, carbon dioxide)
- Serum glucose
- Serum calcium, phosphorous, magnesium, zinc
- Blood urea nitrogen/creatinine
- Serum amylase
- Urine pH and urinalysis
- Electrocardiography

Box 64.5. Medical Complications of Eating Disorders

Associated with Purging Behavior

- Fluid and electrolyte imbalances (from laxative abuse and vomiting)
- Irreversible cardiac muscle damage (from ipecac toxicity)
- Esophagitis, dental erosion, Mallory-Weiss tearing (from chronic vomiting)
- Renal stones (from dehydration)
- Amenorrhea, hypoestrogenemia, osteopenia (from decreased body mass index)

Associated with Caloric-restrictive Behavior and Weight Loss

- Abnormalities on electrocardiography: QTc prolongation, low voltage, sinus bradycardia, sinus tachycardia, segment depression (from electrolyte abnormalities)
- Cardiac arrhythmias, including supraventricular beats and ventricular tachycardia, with or without exercise
- Mitral valve prolapse
- Pericardial effusion
- Delayed gastric emptying, slow gastrointestinal motility, constipation, bloating, fullness, abnormal liver function tests (from fatty infiltration of the liver)
- Increased blood urea nitrogen, increased risk of renal stones, total body depletion of sodium and potassium
- Refeeding syndrome (from extracellular shifts of phosphorous)
- Leukopenia, anemia, thrombocytopenia
- Amenorrhea, hypoestrogenism, osteopenia (from decreased body mass index)
- Growth retardation, pubertal delay
- Cognitive deficits
- Cortical atrophy, seizures

Modified from Rosen DS; American Academy of Pediatrics Committee on Adolescence. Identification and management of eating disorders in children and adolescents. *Pediatrics.* 2010;126(6):1240–1253, and Goldstein MA, Dechant EJ, Beresin EV. Eating disorders. *Pediatr Rev.* 2011;32(12):508–521.

Radiologic studies, such as computed tomography of the head or magnetic resonance imaging of the brain, are indicated if the diagnosis of an eating disorder is uncertain or the neurologic examination is abnormal. Bone density studies, such as dual-energy x-ray absorptiometry scanning, are not performed routinely except in adolescents with sustained amenorrhea for longer than 6 months. If amenorrhea persists, annual dual-energy x-ray absorptiometry scanning is recommended. An upper and lower gastrointestinal series may be warranted in the patient with esophageal symptoms or in whom IBD is a strong consideration. The performance of other procedures, however, should be based on the individual case and associated symptoms.

Management

It is the role of the primary care physician to recognize when inappropriate dieting and weight loss become an obsession for an adolescent and when abnormal and unhealthy behaviors develop for maintenance of obvious malnutrition. When treating the patient with eating disorder, the physician must first establish trust; in doing so, the patient should be reassured that the physician is not attempting to remove all control by trying to make the adolescent "fat." The goal is to create a therapeutic alliance between the physician, adolescent, and family to restore and maintain the patient's health and emotional well-being as well as promote recovery and prevent acute and long-term complications. Depending on the severity of symptoms and the comfort level of the physician to monitor early medical, nutritional, and psychological issues, the adolescent may continue to be followed by the primary care physician in conjunction with a registered dietitian, family therapist, and mental health professional, such as a psychologist and/or psychiatrist. Early in the treatment course, the primary care physician must be willing to follow the patient frequently—as often as once or twice a week, if necessary—depending on the medical and psychological stability of the patient. If the physician wishes to refer the patient to an experienced multidisciplinary team of specialists, it is important that the primary care physician remain informed and involved in the care of the teenager.

Numerous studies have shown that eating disorders are best managed by an interdisciplinary professional team experienced in providing developmentally appropriate care for children and adolescents with eating disorders. This team generally consists of the primary care physician, an adolescent medicine specialist, a psychologist and/or psychiatrist, a registered dietician, and a social worker or case manager. Ideally, the team is available to offer both inpatient and outpatient services, although most mild to moderately affected teenagers can be treated in an outpatient setting. Criteria for inpatient admission should be established by the team and reviewed with the patient and family at the onset of therapy.

Particularly for the patient with restrictive eating disorder, consensus must be reached between the adolescent, parent or guardian, and multidisciplinary team about the minimum acceptable weight for the patient's age, height, pubertal stage, premorbid weight, and previous growth trajectory. Attaining such consensus should be done in conjunction with a registered dietitian. Unlike with adults, weight restoration in the adolescent also must take into account the requirements for normal pubertal growth. An agreement that includes the goals of treatment, parameters for weight gain, and maintenance of health should be established between the adolescent and all members of the treatment team. Refeeding/nutritional rehabilitation must be the initial priority, especially in the adolescent with AN, as long as the patient is otherwise medically stable and does not require inpatient psychiatric hospitalization. Details about the proposed nutritional regimen, which includes a stepwise increase in daily caloric intake, calculated amount of protein to be ingested, daily fat intake, vitamin and mineral requirements, and treatment goal weights, should be developed by the dietitian and reviewed with the adolescent and the family in conjunction with mental health support and close medical follow-up. (See Rome and Strandjord, and Garber and Kohn, in Selected References for a discussion of traditional and newer approaches to refeeding and refeeding syndrome.) Early nutritional rehabilitation and timely medical stabilization are essential to correct the cognitive deficits associated with disordered eating, especially severe restrictive AN.

Historically, adolescent-focused individual therapy with some family support was the cornerstone of treatment for the patient with an eating disorder, particularly AN. Studies in the past 10 years, however, have shown that family-based therapy (FBT), also known as the Maudsley approach, is both effective and superior to individual therapy for AN. Consisting of 10 to 20 family meetings over a 6- to 12-month treatment course, FBT is an outpatient form of family therapy that empowers parents to take charge of their adolescent's weight restoration. Patients with disordered eating often try to hide or minimize their illness and generally have difficulty acknowledging their abnormal eating behaviors, associated patterns, and degree of weight loss. Parents, too, may be in denial or may be unaware of the extent of their teenager's condition. Family-based therapy emphasizes the role of the parents in taking the lead in managing their adolescent's eating, particularly in the early stages of treatment. Therapists assist the family to problem-solve factors that may be perpetuating the eating disorder behaviors and thus interfere with improvement of the adolescent's nutrition and weight restoration. Family-based therapy does not blame the parents for causing the eating disorder; rather, solutions are sought for moving forward. Through a distinct 3-phase structured process, FBT initially focuses on refeeding and weight restoration (phase 1); followed by gradually allowing the adolescent to have more responsibility for eating and weight gain (phase 2); and finally addressing the psychological aspects of the eating disorder in the context of adolescent development and treatment termination (phase 3). It has been reported that weight gain in the first month of FBT is predictive of success with this approach. The primary care physician must work cooperatively with mental health colleagues to provide the necessary structured psychological services for the patient and family. Although the

process is difficult, the patient must begin to acknowledge his or her behaviors and accept the need for assistance before effective mental health interventions can occur.

For those who are not able to participate in FBT, individual therapy, such as cognitive behavioral therapy, should be provided for both the patient and family. Support groups also may be beneficial and frequently are an important component of a day treatment program (eg, day hospitalization, partial hospitalization) for the adolescent with eating disorder who requires more intensive outpatient care but not an inpatient hospitalization or residential program. Day treatment programs are generally less costly and may be more accessible than traditional hospital-based programs. According to the American Academy of Child and Adolescent Psychiatry, psychiatric hospitalization, day programs, partial hospitalization programs, and residential programs should be considered only when outpatient interventions have been unsuccessful or are unavailable. (See Golden et al in Selected References for a discussion of the role of the medical provider at each level of care.)

Pharmacotherapy with agents such as selective serotonin reuptake inhibitors are generally not prescribed for the adolescent with AN except to manage comorbid conditions, such as depression and anxiety disorders. Several studies have shown, however, that these same medications can be effective in patients with BN by decreasing binge-eating and purging behaviors. Randomized controlled trials support the use of fluoxetine, tricyclic antidepressants, or topiramate in the management of BN. Additional benefits are achieved when medication is combined with cognitive behavioral therapy, dialectical behavior therapy, or FBT.

Medical complications of eating disorders are well established (see Box 64.5). Inpatient treatment is required for less than 75% ideal body weight for age, sex, and stature; continued weight loss despite intensive outpatient treatment; or a history of rapid weight loss. Refusal to eat and body fat less than 10% also are criteria for hospital admission. Other indications include cardiovascular compromise, such as bradycardia (<50 beats/minute during the day or <40 beats/minute at nighttime), orthostatic hypotension (changes in blood pressure >10 mm Hg, or pulse >20 beats/minute), or altered mental status; evidence of persistent hypothermia (<35.6°C [<96.1°F]); suicidality (ie, ideation, plan, or attempt) or out-of-control behavior; intractable vomiting; electrolyte disturbances or uncompensated acid-base abnormalities (serum potassium <3.2 mEq/L or serum chloride <88 mEq/L); hematemesis; and significant dehydration as evidenced by systolic blood pressure lower than 90 mm Hg or syncope. Cardiac arrhythmias, including prolonged QTc, also require inpatient monitoring. Rarely does confirmation of the diagnosis warrant an inpatient stay. The goal of hospitalization is to correct medical complications, document appropriate weight gain, and establish healthy and safe eating habits with the assistance of the parent or guardian.

Prognosis

Overall, the outcome for the patient with an eating disorder is variable, with some patients recovering after minimal intervention and with other patients developing more chronic problems. Binge eating, for example, may replace food restriction. Most studies report the prognosis as more favorable if the patient's condition is identified early and treated rapidly and aggressively. Predictors of poor outcome for AN include very low body weight at the time of initial treatment, long duration of illness, a psychiatric comorbidity, a dysfunctional parent-child relationship, and purging behaviors. For BN, factors found to be predictive of poor outcome include longer duration of illness at presentation, severity of eating pathology and frequency of vomiting, premorbid obesity, associated comorbid disorders (eg, personality disorder, substance use), and suicidal behavior. A family history of alcoholism also has been reported as a poor prognostic factor for BN.

According to current literature, eating disorders have the highest mortality of any mental illness. The mortality rate for adolescents with AN is approximately 2%. Higher numbers were previously reported when adult and adolescent data were combined. Exact figures for BN have not been determined, although the mortality rate has been quoted as being similar to that of AN. The most common cause of death in both disorders is suicide. Medical causes are often the result of cardiac arrhythmias from electrolyte abnormalities.

CASE RESOLUTION

Although the adolescent may not currently meet strict criteria for the diagnosis of AN, her preoccupation with dieting in the context of weight loss and a BMI of 17 is worrisome. Your concerns about the patient's documented weight loss, menstrual dysfunction, and current eating and dieting behaviors should be discussed openly with the teenager and her family. General laboratory tests should be performed. The adolescent should be referred to a mental health professional and registered dietician with experience in the management of eating disorders for further evaluation. The emphasis should be on the teenager's overall health and well-being. She should be followed frequently until her weight and eating behaviors have reached the mutually agreed-on goal by all professionals involved in her care, after which she should continue to be seen at regular intervals by her primary care physician.

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CHAPTER 65

Body Modification: Tattooing and Body Piercing

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CASE STUDY

A 16-year-old girl comes to your office for her annual physical examination. Although the girl was previously healthy, her mother is concerned that the girl seems irritable and unwilling recently to participate in family events. The adolescent is currently in 10th grade at a local public school, gets As and Bs in most subjects, is a member of the volleyball team, and has just begun working part-time at a movie theater. Both her parents are employed, and the girl gets along well with her 19-year-old sister, who is currently in college, and her 14-year-old brother. She has many friends in the neighborhood as well as at school.

You interview the adolescent alone and learn that she occasionally smokes marijuana, has tried cocaine on 1 occasion, and attends parties at which many people are drinking alcohol. She has been sexually active in the past but is not currently. She denies depression and describes her mood as generally happy, except when she is forced to spend what she believes is excessive time with her family instead of with friends.

On physical examination, the adolescent's height and weight are in the 50th percentile for age. Her body mass index is 21. Vital signs are normal. You note a small tattoo at her right hip area. The girl's mother is unaware of its presence, according to the teenager. She obtained it a few months prior while visiting her sister in college.

Questions

1. What is the epidemiology of body modification in adolescents and young adults?
2. What is the motivation for obtaining tattoos and body piercing in this age group, and is there an association with high-risk behavior?
3. What techniques are used to place tattoos and perform body piercing?
4. What are possible adverse consequences of body modification, and what should be done to manage them?
5. How can the primary care physician assist an adolescent in making a safe and healthy decision about body modification?

Body modification is the practice of permanently altering one's appearance, and it has been practiced in many cultures worldwide for millennia. Such modification includes tattooing, body piercing, and scarification. Although much less common than tattooing and body piercing, scarification uses various techniques to intentionally irritate the skin to produce a permanent pattern of scar tissue. It is described as a more intense form of body modification and is reportedly appealing to individuals seeking a more dramatic result.

Historically, body modification, particularly tattooing, was associated primarily with the military and with disenfranchised individuals, such as criminals and gang members. Currently, however, it is considered mainstream among many individuals in US society, with people of all ages as well as socioeconomic and educational backgrounds sporting tattoos and piercings. Body art is seen in most clinical settings serving youth and young adults as well as in middle schools and high schools and on college campuses. Additionally, it is not uncommon to encounter a teenager with multiple tattoos and body piercings or to evaluate an adolescent for a possible complication of the procedure. Whether described as a rite of passage, an expression of their own individuality, or a desire to join a particular peer group, obtaining a tattoo or body piercing has become a widespread experience during adolescence and young adulthood and therefore should be added to the primary care physician's list of issues to review with the teenager during the routine health maintenance visit.

The practice of typical body modification should be distinguished from more intense nonsuicidal self-injurious behaviors, such as cutting, scratching, burning, and hitting oneself. The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) describes *nonsuicidal self-injury disorder* (NSSID) as a mental health disorder associated with self-injury that can manifest in impulsive or compulsive adolescents suffering from anxiety, depression, personality disorders, or psychotic disorders. Adolescents engaged in self-injury expect to gain relief from their negative emotions through physically hurting themselves and may use this behavior as a means of coping with personal emotional issues. Consultation with a mental health specialist is warranted for these challenging cases.

Epidemiology

It was previously estimated that 13% to 25% of the general population in the United States had a tattoo. Because tattooing has grown in popularity and become a fast-growing retail business, however, these figures are likely a gross underestimation. Surveys conducted in outpatient clinics and on high school and college campuses confirm that more than 10% to 15% of teenagers aged 12 to 18 years have a tattoo. In a study of more than 2,000 US high school students, 55% expressed interest in obtaining a tattoo regardless of its permanence or the students' academic success in school. Additionally, it has been reported in the literature that one-half of new tattoos are obtained by women and that many are obtained during the college years. Surveys conducted in the last 10 years reveal that approximately 20% to 25% of college students have a tattoo.

Body piercings are more common than tattoos among adolescents and young adults, and some experts speculate that this may be because the procedure is not permanent, allowing the individual to remove the jewelry at any time. In a study of college students, 45% had undergone body piercing and 22% had tattoos with and without piercings. Other studies that include younger adolescents attending an outpatient adolescent clinic report body piercing in approximately 27% and tattoo in approximately 13%. Most studies also confirm that females are more likely to obtain a piercing than males; male athletes are more likely to obtain a tattoo than their nonathlete male counterparts.

The motivation for obtaining body art also has been studied, with most of the literature confirming adolescents' search for uniqueness and desire to enhance their independence and self-identity. For some teenagers, body art is considered a form of decoration or an opportunity to be creative; alternatively, it fulfills a desire for peer acceptance and solidifies group membership. Attainment of body art for the purpose of peer acceptance or solidifying group membership has been documented by studies demonstrating that friends or peers provide the strongest influence for youth pursuing body art. Tattoos in particular can be a means of permanently documenting a relationship with an individual or group. Despite popular belief, studies do not confirm that most adolescents obtain a tattoo or body piercing impulsively while under the influence of illicit drugs or alcohol. In fact, many older teenagers and young adults report taking considerable time to decide whether to obtain a tattoo or piercing.

The extent to which parents or guardians are involved in the adolescent's decision to have a tattoo placed or body piercing performed is variable for many teenagers and depends on their particular relationship, whether the adolescent is a minor, and state parental consent requirements. In some cases, parents are not consulted before the procedure, although in many states the law requires parental consent and presence, and tattooing of minors is prohibited. Current laws are not consistently enforced, however, and in many states tattooing and body piercing have different regulations. Health professionals are therefore encouraged to become familiar with their individual state laws related to minors obtaining tattoos and piercings to counsel their patients appropriately.

Clinical Presentation

Tattoos can be found on any area of the body and, depending on the talent of the artist and the desire of the client, can be simple and 1 color or quite elaborate and multicolored. Generally, amateur tattoos (ie, those performed by a nonspecialist or friend) are less intricate and are considered more risky because often they are not performed under ideal circumstances, using antiseptic techniques, or with conventional pigments and applicators. Unconventional pigments include charcoal, India ink, and mascara. Pencils, pens, sewing needles, and other sharp objects, including guitar strings, may be used to apply the dye for a self-administered or amateur tattoo.

The most common site for piercing is high on the pinna of the ear. Regular lobular ear piercings are not generally included in the context of body modification because they occur commonly at any age. Other body sites that are pierced include the tragus of the ear, eyebrows, tongue, nose, nasal septum, cheek, lip, navel, and nipples. Intimate or genital piercings also can be seen in males and females. The foreskin, penis, scrotum, clitoris, perineum, and labia are all common areas for intimate piercings. Although specific data by sex are not available, it is reported that more men than women obtain genital piercings.

Technique, Application, and Safety Standards

Tattoos

The process of applying a professional or commercial tattoo is relatively standardized, although different tattoo parlors may have their own individual practices. Generally, the client selects a design from flash sheets in the shop or an individualized design by the artist, and the tattoo is stenciled or drawn on clean-shaven skin. The skin is cleansed again with an antiseptic solution, and a thin layer of ointment, such as petroleum jelly, is placed on the site. Most professionals in the United States use a motorized, electric-powered tattoo gun, which is similar to a dental drill, that holds 1 or several needles in a needle bar that is dipped in ink and that punctures the skin a few millimeters deep, up to several thousand times a minute. In Europe, small amounts of ink are applied directly to the skin and the needle is used to push the ink into the skin. Regardless which method is used, the pigment reaches the level of the dermis via the solid-bore needle or needless, while blood and serosanguineous fluid are wiped away as tattoo placement continues. When the tattoo is completed or the session is finished, an antibiotic ointment is applied and a bandage is placed over the site.

The client is instructed to remove the dressing 24 hours later and keep the area moist with an antibiotic ointment. Additionally, clients are instructed to place an emollient or vitamin E oil over the healing tattoo several times a day. The area is to be cleansed with a mild soap and patted dry or blotted (not rubbed). If aftercare instructions are followed carefully, most tattoos heal in approximately 2 to 3 weeks, with superficial crusting and "shedding" of epidermis as part of the natural course of tattoo placement. Sunscreen should be worn if sun exposure cannot be avoided in the ensuing weeks.

Swimming, soaking in water, and direct shower jets to the area are discouraged for several weeks.

Ideally, the application process uses inks that are poured into single-use disposable containers and sterile needles that are disposed of after each client. Although the tattoo ink pigments are considered cosmetics and are subject to US Food and Drug Administration regulation, however, neither the tattooing process itself nor the use of the inks is regulated. Additionally, certain pigments may not be approved for intradermal use and have been known to contain low concentrations of metal salts, such as lead, iron, mercury, or aluminum.

The practice of universal precautions is required by state and local regulatory agencies and advocated by specific educational groups, such as the Alliance of Professional Tattooists (APT), a nonprofit organization established in 1992 to promote standards for professional and associate tattooists and develop guidelines for consumers to evaluate the safety of individual tattooing establishments. The organization also sponsors regular educational seminars for tattoo artists on the prevention of disease transmission in tattooing. Membership in APT is voluntary and requires that the professional tattooist pay annual dues, participate in a health and safety seminar, and have at least 3 years of full-time experience at a consistent location. Other membership levels are available, with variable costs for annual dues and requirements for membership (eg, <3 years' experience and/or apprenticing associates). Despite APT efforts and standards, however, specific areas of concern about the tattoo industry remain, including unlicensed tattoo artists and establishments, the presence of unregulated ingredients in the pigments, inconsistent cleaning of equipment between clients, an inability to reliably sterilize all parts of the equipment despite good efforts, and infrequent inspections of tattoo parlors by regulatory agencies.

Body Piercing

The process of body piercing is generally less complicated than tattooing and depends, in part, on the anatomic site to be pierced. The client chooses the jewelry and body part to be pierced, the area is cleaned with a topical antiseptic, and a large hollow needle is brought through the skin. The jewelry is then brought through the hole following the needle, and the hole is sealed with a bead, bar, or metal disc. Because the procedure is relatively quick, topical anesthetics are generally not required.

Although earlobe piercing is a relatively straightforward procedure, it is commonly performed using a piercing gun at a local mall, cosmetic shop, or kiosk. Because the stud is driven through the earlobe via the gun rather than through a hollow tube manually, the tissue is torn or crushed rather than pierced. Additional concerns about the piercing gun include inconsistent and informal training of personnel, an inability to sterilize all parts of the gun between procedures, and embedded earrings and ear backs. The gun cannot be adjusted for the thickness of other tissues, so although it is a popular method for earring placement, this tool is not recommended for sites other than the earlobe.

The immediate aftercare of piercing varies by the site pierced. For example, local skin discoloration and a nonmalodorous serous exudate can occur with piercings of the nares or navel. Tongue or lip piercings have been associated with significant swelling for several days after the procedure. Additionally, a yellow-white fluid secretion can occur that, to the unfamiliar examiner, appears to mimic an infection. Clients with oral piercings are generally instructed to dissolve ice in their mouth immediately after piercing to help with pain and swelling, manage further discomfort with a nonsteroidal anti-inflammatory drug, and elevate the head when sleeping.

Healing times vary considerably depending on the anatomic site of the piercing. Generally, sites with increased vascularity and exposure (eg, face, tongue) tend to heal faster than those involving cartilage, which is poorly vascularized. Areas of the body that are subject to movement also heal more slowly. For example, healing time may be 1 to 2 months for the tongue, 1 to 1.5 months for the nasal septum, 2 to 3 months for the nostril, and 2 to 4 months for the tragus of the ear. High-ear piercings through the cartilage also may require 2 to 4 months for healing. Navel piercings have the longest healing time (up to 9–12 months) because of friction and moisture from clothing and often are associated with the most complications.

As with tattooing, not all states have regulations and safety standards in place for body piercing, and if such regulations and safety standards do exist, local governing bodies do not consistently enforce them. Universal precautions should be strictly practiced, and the adolescent should be familiar with these guidelines and know how to find a reputable piercer before obtaining body art.

Because no formal training programs exist for piercers, many learn by video or apprenticeship. Generally, practitioners in studios have completed an apprenticeship and have more training than those in cosmetic shops, malls, or ear-piercing kiosks. They also are more experienced in piercing sites other than the ears and may be members of the Association of Professional Piercers (APP). Established in 1994, the APP is a nonprofit organization dedicated to the education, health, and safety of body piercing for the public. It has developed self-regulatory policies for the industry, standards for membership in the organization, and annual conferences on health and safety issues. Members must have at least 1 year of piercing experience, documented training in blood-borne pathogens and cardiopulmonary resuscitation, and certification in first aid. Members also must show photographic proof of a medical-grade autoclave in the piercing studio and send in spore test results from the autoclave. To help document this, a detailed video of the studio is required, along with copies of all aftercare education given to clients. After this process is completed, the member receives a certificate to mount in the studio.

Current legislation addressing minors and piercing is regulated by individual states; in some states, such as California, ear piercing performed with piercing guns is excluded from the definition of body piercing. Concerning minors, the APP requires that the parent or legal guardian as well as the minor show proof of identification before signing the consent form for body piercing. Additionally, nipple or genital piercings are not performed on anyone younger than 18 years.

Evaluation

History

All teenagers should be interviewed alone, after their parent or legal guardian has had an opportunity to discuss their concerns with the health professional (see Chapter 4). A visible tattoo or body piercing allows the physician to inquire about the circumstances surrounding the body art at the beginning of the interview, in contrast to body art noted in an inconspicuous area of the body during the physical examination. Whether parental consent was obtained before the procedure should be addressed directly, because this issue could be a basis for current as well as future familial conflict. The type of facility in which the tattoo or piercing was obtained should be discussed, along with whether the adolescent recalls whether universal precautions were followed. A general review of systems should be performed to exclude systemic conditions, such as viral hepatitis, as well as any other complications related to obtaining the tattoo or piercing in a nonprofessional environment. Specific questions about the area of the body that is pierced also should be reviewed (Box 65.1). For example, the teenager with a tongue piercing should be asked if he, she, or they has problems with mastication, swallowing, loss of taste or movement, or permanent numbness.

It has been reported that amateur or self-administered tattoos are associated with increased high-risk behaviors, including substance abuse at a younger age, illicit drug use, lower academic achievement, and an increased number of tattoos overall. Recent studies have shown, however, that not all adolescents and young adults with multiple tattoos or body piercing(s) engage in high-risk behavior (Box 65.2). Successful academic achievement and close family support have been reported in tattooed and nontattooed college students. Although tattoos are permanent, more than 50% of academically successful high school students with consistently good grades have reported an interest in them.

Box 65.1. What to Ask

Tattoos and Body Piercing

- When was the tattoo or body piercing placed?
- Did the teenager obtain consent from the parent or legal guardian before getting the tattoo or piercing?
- Is the adolescent satisfied with the tattoo or piercing?
- Was the tattoo or body piercing placed by a professional or by a friend, acquaintance, or relative?
- If the tattoo or body piercing was obtained in a studio, where was the studio located? Was it licensed? Was it clean, "like a medical facility"?
- Did the tattooist or piercer wash his, her, or their hands before gloving? Use new disposable gloves? Open all equipment in front of the teenager?
- For tattoos, did the tattooist remove a sterile needle and tube set from a new envelope? Did the tattooist pour fresh ink in a new disposable container?
- For body piercing, did the piercer use individually wrapped sterile needles? Did the piercer use a piercing gun?
- Did the teenager receive aftercare education, including written material?

Box 65.2. The Association Between Body Modification and High-Risk Behavior in Teenagers[a]

- Adolescents with tattoos or body piercings were found to be more likely to have engaged in risk-taking behaviors than those without either type of body modification. Risk-taking behaviors included disordered eating behavior, gateway drug use (ie, cigarettes, alcohol, marijuana), hard drug use (ie, cocaine, crystal methamphetamine, ecstasy), sexual activity, and suicide. Additionally, aggressive and violent behavior was associated with males having tattoos and with females having body piercings. Gateway drug use was associated with younger age of tattooing and body piercing.[b]
- Adolescents with body modification had 3.1 times greater odds of problem substance use compared with those without body modification.[c]
- Tattooing was significantly associated with older age, living in a single-parent household, and lower socioeconomic status. Such adolescents also exhibited greater involvement in sexual intercourse, higher levels of substance abuse themselves as well as among their peers, increased violent behaviors, and school problems.[d]
- A correlation was found between body piercing in teenagers and increased rate of sexual intercourse, smoking, marijuana use, school truancy, running away, suicidal ideation or attempts, and peer substance use.[e]

[a] Many studies have been conducted to explore the association between high-risk behavior and body modification in adolescents. No definitive answers exist, but this box presents published findings from the early 2000s.

[b] Carroll ST, Riffenburgh RH, Roberts TA, Myhre EB. Tattoos and body piercings as indicators of adolescent risk-taking behaviors. *Pediatrics.* 2002;109(6):1021–1027.

[c] Brooks TL, Woods ER, Knight JR, Shrier LA. Body modification and substance use in adolescents: is there a link? *J Adolesc Health.* 2003;32(1):44–49.

[d] Roberts TA, Ryan SA. Tattooing and high-risk behavior in adolescents. *Pediatrics.* 2002;110(6):1058–1063.

[e] Armstrong ML, Roberts AE, Owen DC, Koch JR. Contemporary college students and body piercing. *J Adolesc Health.* 2004;35(1):58–61.

Whether body art is considered an expression of individuality, rebellious behavior, or succumbing to peer pressure, the presence of a tattoo or body piercing on an adolescent warrants an in-depth psychosocial assessment and review of systems for possible exposure to viral infections, such as hepatitis C.

Physical Examination

In most adolescents with a tattoo or body piercing the routine physical examination is generally normal, unless either a past complication with the tattoo or piercing occurred or a current problem exists. Poor aftercare and hygiene can prolong healing time in body piercings. Additionally, smoking can delay the healing time associated with oral piercings. If the teenager has recently undergone a tongue piercing, a larger barbell will be seen through the tongue. Larger barbells initially are placed with tongue piercing to accommodate the swelling associated with the procedure. Later, the barbell is replaced with a shorter rod.

Infectious and noninfectious complications from tattoos and body piercings are listed in Box 65.3. Local infection occurs in only

Box 65.3. Complications of Tattoos and Body Piercing: Infectious and Noninfectious

Tattooing Complications

Infectious

Bacterial etiologies

- Local skin infections
  - — Superficial pyoderma
  - — *Staphylococcus aureus*
  - — *Streptococcus pyogenes*
- Systemic infections
  - — Deep or severe pyoderma
  - — Syphilis
  - — *Mycobacterium tuberculosis*
  - — *Mycobacterium leprae*
  - — Nontuberculous mycobacteria
  - — *Mycobacterium chelonae*
  - — *Mycobacterium abscessus*
  - — Chancroid
  - — Tetanus
  - — Endocarditis

Viral etiologies

- Human papillomavirus
- Hepatitis B and C
- HIV

Noninfectious

- Hypersensitivity to dyes or pigments
- Allergic granulomas
- Malignant melanoma and basal cell carcinoma at tattoo site
- Keloid formation
- Swelling and burning during magnetic resonance imaging

Body Piercing Complications

Infectious

Bacterial etiologies

- *S aureus*
- *Pseudomonas aeruginosa*
- Group A β-hemolytic streptococcus
  - — Cellulitis
  - — Septic arthritis
  - — Acute glomerulonephritis
  - — Erysipelas
  - — Endocarditis
- *M tuberculosis*
- *Clostridium tetani*

Viral etiologies

- Hepatitis B and C
- HIV

Noninfectious

Body jewelry, in general

- Artifact on radiographs

High-ear piercing

- Pinna deformity

Tongue piercing

- Airway obstruction
- Chipped/cracked teeth
- Interference with mastication/swallowing
- Permanent numbness
- Articulation disorders
- Loss of taste/movement
- Oral mucosa inflammation

Lip piercing

- Injury to salivary ducts
- Aspiration of jewelry

Navel piercing

- Allergic dermatitis

Nipple piercing

- Trauma/avulsion of nipple

Genital piercing

- Tissue inflammation in sexual partner
- Scarring
- Interruption of urinary flow in males

approximately 5% of tattoos, but infectious complications have been reported in as many as 30% of body piercings. Acute signs of infection include erythema, warmth, swelling, and pain at the site, in addition to drainage in some cases. Rarely, a fluctuant, fluid-filled mass is evident if an abscess has developed.

Because some of the noninfectious complications can be related to the type of metal found in the jewelry, knowledge of this specific information is useful in individuals with body piercing. Only jewelry made from surgical stainless steel, titanium, solid 14- or 18-karat gold, or solid platinum should be used in healed piercings to avoid allergic dermatitis. Certain metals, such as nickel, cobalt, and chromium, have been associated with the development of contact dermatitis in sensitive individuals. Initially, during the healing phase of piercings, however, surgical stainless steel and 14-karat gold jewelry should be avoided because they may contain trace amounts of nickel. Permanent makeup also has been reported to cause severe allergic contact dermatitis that can take months to years to completely heal. The reported reactions included tenderness, itching, and "bumps" at the site of the permanent makeup application. Hypersensitivities to dyes or pigments from a professional tattoo also can appear as an erythematous outline of the original work. This inflammatory reaction can also occur with temporary tattoos created with henna, which is approved as a hair dye but is not approved for use on the skin. Use of henna has been associated with severe contact dermatitis, especially if an additive containing paraphenylenediamine is mixed with the henna to give the normal red-brown paste an additional black-and-blue color. The addition of paraphenylenediamine to the henna mixture also speeds drying time and prolongs skin pigmentation.

Keloids and hypertrophic scars can appear as a flesh-colored mass at the area of the tattoo or piercing and differ in their timing and resolution. A hypertrophic scar generally appears within 6 weeks of the tattooing or piercing, is confined to the wound margins, and has a tendency for spontaneous regression. In contrast, keloid formation may occur as late as 1 year after the initial wound, often grows beyond the border of the wound, and persists. Keloids occur primarily in black and Asian patients and can cause an itching or burning sensation that may warrant a prompt referral for removal.

Laboratory Tests

Generally, laboratory studies are not necessary if the adolescent is not engaged in high-risk behavior and is certain that universal precautions were followed when the tattoo or piercing was placed. In most cases, however, the teenager may be uncertain or may not remember the details. In such cases, a serum test for viral hepatitis B and C should be obtained, because hepatitis C virus is found in approximately 30% of people with tattoos, compared with 3.5% of people without them. An antibody test for HIV should be sent for the high-risk teenager who is being screened for other sexually transmitted infections; however, the test is not necessary if the patient has a tattoo or body piercing and no other indications for HIV screening.

No definitive documented cases of HIV transmission from tattooing or body piercing have been reported to date.

A serum test for syphilis should be done because, unlike HIV, transmission of this and other sexually transmitted infections has been reported from tattooing or piercing, albeit rarely.

If evidence exists of abscess formation, such as may be seen with perichondritis, a specimen of the purulent fluid should be obtained and sent for culture and antimicrobial sensitivities.

Management

Although tattoo removal or modification is not ordinarily requested by most adolescents, it is available for the patient who no longer wants the tattoo or is unhappy with its current appearance. Recent studies have examined the motivation for tattoo removal after a duration of at least 10 years. Reasons for removal are varied and include embarrassment, a need to disassociate from the past, improved self-esteem, being tired of the tattoo, and negative social remarks about the tattoo. Professional employment or job advancement was not consistently cited as a common reason for removal, although some surveys attribute tattoos in certain visible locations as career limiting.

Historically, tattoo removal was quite difficult, and only approximately 70% of tattoos could be completely cleared because of impurities in tattoo pigments, different ink densities and depths, and the presence of certain metals in the dyes. *Selective photothermolysis*, which is a newer technology that uses a selective type of laser to target specific color pigments, is quite effective in removing several ink colors. Using a quality-switched laser system, the wavelength of the laser is set to match the specific absorption pattern of the different color pigments in the tattoo and a pulse is delivered over nanoseconds with extremely rapid heating. Fragmentation of the tattoo pigment occurs and, upon releasing it into the skin, an acute inflammatory process follows along with phagocytosis of fragmented pigment particles. Subsequent laser treatments can be performed 4 weeks later, although longer intervals between treatments may reduce the risk of permanent changes to the pigment of the skin. No laser method is completely successful in removing all evidence of the tattoo, especially intricate and colorful ones, and in most cases, immediate lightening of the skin occurs with subsequent hypopigmentation. Hyperpigmentation, allergic reactions, and scarring resulting from thermal burn injury may also occur after laser treatment. Although these complications are usually transient, they can be permanent, and the patient must be made aware of the risks associated with each process. Tattoo removal can be costly. Whereas the average cost for tattoo placement may be $50 to $100 per hour of service, removal may cost several thousands of dollars depending on the size, complexity, and number of colors in the tattoo. Other, less popular techniques for tattoo removal include dermabrasion, which is less desirable because of concerns for infection and its variable effectiveness; *salabrasion* (ie, use of a salt solution to abrade the skin); scarification; and surgical excision, with or without the use of tissue expanders and grafting. Camouflaging also can be performed; with this technique, either a new pattern is made using skin-toned pigments or the tattoo is modified and made into another design. For instance, the name of a person can be incorporated into a new tattoo of an animal or object. Certain nonprofit organizations also offer tattoo removal to former gang members as a part of their preparation for employment and educational services.

Although it seems counterintuitive, in most cases removal of jewelry is not recommended if a piercing appears infected. The concern is that, without a wick or surgical drain, any potential space left at the site after the jewelry is removed could result in the development of an abscess. Instead, the adolescent should be instructed to leave the jewelry in place to allow drainage of the wound, use warm compresses, and clean the area with an antimicrobial soap and water. The use of topical antibiotic ointments is controversial because they can be occlusive and contribute to delayed healing. Certain individuals with specific medical conditions are at increased risk for infections after body piercing, including patients with diabetes mellitus, systemic lupus erythematosus, and conditions requiring chronic corticosteroid use. In such cases, if infection occurs it may be necessary to remove the jewelry early in the course of the infection and initiate appropriate antibiotic coverage.

Oral antibiotic coverage against skin staphylococcal and streptococcal species should be administered if the tattoo or piercing appears superficially infected and other measures have not been effective. More aggressive treatment is required if the piercing site involves the cartilage, such as with high-ear piercings, or if the patient is immunocompromised. Auricular infections can occur even after the use of strict antiseptic techniques and may appear a few weeks after the initial piercing. The cartilaginous helical area of the ear is particularly prone to infection because it is poorly vascularized and is slow to heal. Additional antimicrobial coverage against *Pseudomonas aeruginosa* is essential in these cases, along with diligent follow-up to monitor the initial response to oral antibiotic therapy. Currently, oral fluoroquinolones offer good antipseudomonal and antistaphylococcal coverage and penetrate cartilage well. Inpatient hospitalization for intravenous antimicrobial therapy and subsequent drainage of the site may be necessary for moderate or unresponsive infections. Early recognition of perichondritis and appropriate management of it are essential to prevent the development of a persistent infection and to minimize the risk of a permanent auricular deformity. Additionally, timely consultation with a plastic surgeon or otolaryngologist early in the course of the suspected infection is recommended for early incision and drainage of a perichondral abscess, appropriate wound care, and possible reconstruction of any disfigurement. Additional information about body piercing complications and their management in adolescents and young adults can be found in the 2017 American Academy of Pediatrics Committee on Adolescence article on tattooing, piercing, and scarification in that population.

Role of the Primary Care Physician

Education is essential for the adolescent who has not yet obtained a tattoo or piercing or who already has one and is contemplating the placement of another. The physician should inquire where the

adolescent plans to have the procedure performed and educate the patient on what key questions to ask and how to find a reputable studio. Additional information, such as the APT (www.safe-tattoos.com) and APP (www.safepiercing.org) websites, should be shared with the patient, and written materials that contain safety guidelines should be provided to the adolescent at the visit. Teenagers are often reluctant to ask their health professionals for information about obtaining tattoos and piercings and almost never contact a health professional if they believe they may have a complication associated with tattooing or piercing. Instead, they tend to ask their peers or contact the establishment at which the tattoo or piercing was initially obtained. Primary care physicians should be a nonjudgmental resource during health maintenance visits to ensure the adolescent's continued health and safety. Additionally, the appearance of an uncommon medical condition, such as unexplained hepatitis, endocarditis, or toxic shock, in the adolescent patient or young adult warrants careful consideration for a possible complication related to tattooing or body piercing.

Prognosis

Most teenagers and young adults experience no adverse effects from body modification. Complications are uncommon with the placement of a professional tattoo but can occur with body piercing and usually are amenable to medical management. Risk-taking behavior that may occur in conjunction with body modification can carry long-term sequelae, but the association between defiant behavior and having a tattoo has changed over time. Although body modification has become more widespread and generally is acceptable based on public opinion, any decision to pursue body modification should be made in the context of the adolescent's long-term and professional career goals, because studies have documented negative repercussions in some areas of employment.

CASE RESOLUTION

Because the presence of 1 tattoo may be associated with a likelihood to obtain another tattoo, the primary care physician should review safety guidelines for obtaining a tattoo and body piercing with the adolescent and offer the teenager educational material or refer her to select websites to reinforce the discussion. The immunization status of the teenager also should be assessed, with particular attention to tetanus and hepatitis A and B. Additionally, in private discussion with the teenager, the physician should reiterate any concern about the adolescent's current high-risk behavior and its possible consequences. It also may be worthwhile to discuss with the teenager the pros and cons of telling her parents about the tattoo before they find out inadvertently.

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CHAPTER 66

Depression and Suicide in Adolescents

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CASE STUDY

A 15-year-old girl is brought to your office by her mother with the chief report of easy fatigability. The mother is concerned because her daughter is always tired, although several other physicians have told her that the girl is healthy. The adolescent, who states no complaints or concerns, appears quite shy. She is currently in the 10th grade, likes school, receives average grades, and speaks English and Spanish. The mother, a single parent, moved to the United States from El Salvador approximately 2 years ago with her 2 daughters. Currently, they are living with relatives in a two-bedroom apartment. The mother is employed as a housekeeper, and the patient and her sister help their mother clean homes on weekends. During the week they make dinner for the rest of the family as a means of contributing to the rent. When you speak to the girl alone, she acknowledges she has a few friends at school and adamantly denies any drug, alcohol, or tobacco use. She has never been sexually active and reports no history of sexual or physical abuse. She scores 11 on the 9-item Patient Health Questionnaire. The physical examination is entirely normal, although the girl's affect appears somewhat flat.

Questions

1. What is the significance of nonspecific symptoms, such as fatigue, during adolescence?
2. What factors contribute to depression in the adolescent?
3. What are the classic signs and symptoms of depression in the adolescent?
4. What are some important points to cover in the history when interviewing the adolescent with suspected depression?
5. What is the purpose of the depression/suicide screening tool (eg, Patient Health Questionnaire-9)? How should the results be interpreted and used?
6. How is the risk of suicide assessed in the adolescent patient?
7. How should suicidal behavior (ie, suicide attempts) be managed in the adolescent?

The number of people in the United States with mental health concerns, including depression and suicidality, far surpasses the number of mental health specialists. For this reason, the American Academy of Pediatrics recommends that primary care physicians take an active role in the identification and early management of uncomplicated mental health concerns in children and adolescents. Furthermore, the importance of primary care physicians in this arena is emphasized by research findings. Patients who ultimately die by suicide visit primary care physicians more than twice as often as mental health clinicians in the months leading up to their death. A review of studies analyzing this clinical scenario estimated 45% of those who died by suicide saw their primary care physician in the month before their death, whereas only 20% saw a mental health professional in the preceding month. Women and older patients are more likely to have sought care in the month before their suicide compared with men and younger patients. Those who practice general medicine (ie, internists, pediatricians, family physicians) write most of the antidepressant prescriptions in the United States.

Depression and suicidality are common in the pediatric and adolescent population. Thus, it is important to remain cognizant of their clinical presentation and to diligently screen and probe for their presence.

Depression is among the multiple risk factors that predispose adolescents to suicide. Not all teenagers who attempt suicide are depressed, however; conversely, not all depressed adolescents attempt suicide. This distinction is important to keep in mind when evaluating any adolescent for depression or suicidal behavior. Early identification of risk factors in the susceptible adolescent along with early intervention for those with depressive symptoms will, it is hoped, benefit the teenager at risk for suicide and allow the primary care pediatrician to provide first-line intervention for the adolescent patient experiencing emotional distress.

Epidemiology

Depression

The exact prevalence of depression in adolescents is difficult to determine because depression is often underreported. It is considered 1 of the main psychiatric conditions affecting children and adolescents, however, along with anxiety. Depressive symptoms have been reported in as many as 50% of girls and 40% of boys in the 14- to 15-year age group. The overall prevalence of depression as an illness is approximately 5%; mild depression is reported in 13% to 28% of teenagers, moderate depression in 7%, and severe depression in 1.3%. Depression occurs more commonly in adolescents than in prepubertal children and is more frequent in females than males after puberty.

Several risk factors contribute to the development of depressive disorders in adolescents (Box 66.1). Certain psychiatric conditions also are associated with depression, including generalized anxiety disorders, eating disorders, substance abuse, conduct disorders, and borderline personality disorders.

Suicide and Suicidal Behavior

Suicide is the second-leading cause of death in the United States in individuals 10 to 24 years of age; only motor vehicle crashes result in more deaths in young people. In 1960, the annual suicide rate in this age group was 5.2 per 100,000. The suicide rate has continued to rise over the past 50 years. According to the Centers for Disease Control and Prevention, the suicide rate in 2017 was 11.8 per 100,000, with 6,241 completed suicides in 15- to 24-year-olds. It has been stated that for every suicide that is completed successfully, 50 to 100 suicides are attempted. More than 75% of teenagers who committed suicide had not been on medication and were not under treatment for depression or suicidal concerns.

According to the 2017 Youth Risk Behavior Survey of the Centers for Disease Control and Prevention, 17.2% of all students in grades 9 to 12 nationwide had seriously considered attempting suicide during the previous 12 months. Approximately 14% of students nationwide had made specific suicide plans, more than 50% of students with suicide plans reported attempting suicide, and 2.4% of the individuals who attempted suicide required medical attention. The prevalence of developing a suicide plan was higher among gay, lesbian, and bisexual students (38.0%) and "not sure" youth (25.6%) than among heterosexual students (10.4%). Rates also differ by race and ethnicity, with black and Asian teenagers having lower suicide rates than white teenagers, and black females having the lowest suicide rate of all adolescents. American Indian/Alaska Native males have the highest suicide rate among this age group.

In discussing adolescent depression and suicide, it is important to clarify the meaning of specific terms. *Suicidal ideation* is thoughts of engaging in suicide-related behavior. *Suicidal intent* is having the aim or resolve to follow through with a plan. *Suicidal behaviors* are behaviors related to suicide, including preparatory acts, suicide attempts, and death. *Suicide attempt* is a nonfatal, self-directed, potentially injurious behavior with any intent to die as the result of the behavior. A suicide attempt may or may not result in injury. *Suicide* is death caused by self-directed injurious behavior with any intent to die as the result of the behavior.

Several risk factors associated with adolescent suicide have been identified (Box 66.2). Suicide is rarely associated with depression but is most often associated with a recent, abrupt crisis (eg, breakup of

Box 66.1. Risk Factors Associated With Depressive Disorders in Adolescents

- Family history of psychiatric illness (eg, parent with an affective condition, another family member with a bipolar or recurrent unipolar disorder)
- Age at onset of depression in the affected parent; the earlier the age of onset, the greater the likelihood of depression in any children
- Exposure to an unexpected suicide attempt or completion in the school or community
- History of environmental trauma (eg, sexual or physical abuse, loss of a loved one)
- Chronic illness
- Certain medications (eg, propranolol, phenobarbital, prednisone)

Box 66.2. Risk Factors Associated With Suicide in Adolescents

- History of a previous suicide attempt (most important)
- Male sex
- History of adoption
- Lesbian, gay, bisexual, or questioning sexual orientation
- Transgender identification
- History of physical and/or sexual abuse or exposure to violence
- Family history of psychiatric disorders, especially depression, substance abuse, and suicidal behavior
- Personal mental health problems
  - Sleep disturbances
  - Psychological characteristics, such as aggression, impulsivity, and hopelessness or severe anger
  - Preexisting psychiatric condition (eg, depressive/bipolar disorder, conduct disorder, posttraumatic stress disorder)
  - Alcohol and illicit substance abuse or dependence
  - Pathologic internet use
- Social and environmental issues
  - Family disruption or stressful life event, including violence, divorce, or death of a loved one
  - Impaired parent-child relationship
  - Living outside the home (eg, homeless, corrections facility, group home)
  - Bullying
  - Exposure to an unexpected suicide attempt or completion in the school or community
  - Availability of firearms in the home

a romantic relationship, accusation, failure). Although adolescent females are more likely to attempt suicide than males (22% and 12%, respectively), males are more likely to succeed (male-to-female ratio, 4:1). This fact may result from the lethality of the methods, such as firearms or hanging, that males usually choose. Although females are more likely to ingest pills, the role of firearms in suicide attempts or completion in females is increasing. The availability of firearms and alcohol, which varies from state to state, greatly contributes to the occurrence of suicide. Up to 45% of individuals who have committed suicide show some evidence of intoxication at the time of death. Although most suicide attempts are impulsive, studies have shown that adolescents often have communicated their suicidal intent or ideation to someone before the attempt. Approximately 50% of adolescents who attempt suicide have sought medical care within the preceding month and 25% within the preceding week. In contrast, only one-third have previously received mental health care.

Clinical Presentation

The depressed or suicidal adolescent may visit a physician for a variety of clinical reasons, but rarely do they seek professional assistance for feeling "depressed." Some adolescents have a difficult time accurately understanding and communicating their emotions. A depressed teenager often presents as irritable, argumentative, or angry rather than sad. Teenagers may exhibit diminished interest or pleasure in activities or relationships and changes in cognitive functioning (eg, concentration), sleep, appetite, or energy, which results in impairments in multiple activities of daily living. They also may present with seemingly nonemergent complaints and a flat affect or with multiple somatic concerns and an anxious appearance. Additionally, the teenager may have frequent visits to the primary care physician's office for acute conditions that on first glance seem unrelated but later indicate possible substance abuse or a mood disorder. Some adolescents are accompanied by a family member or friend, which initially may make the teenager reticent to discuss psychosocial issues with the physician. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (*DSM-5*), major depressive disorder (MDD) is diagnosed when at least 5 of 9 listed symptoms or signs occur for a duration of at least 2 weeks. At least 1 symptom must be sadness or loss of interest for most of every day, and a significant change in function must exist. Changes can manifest as poor academic performance; school attendance issues, including truancy and disruptive behaviors; and difficulties with peer and familial relationships (Box 66.1).

Pathophysiology

The exact neurobiologic etiology of depression remains elusive. It is believed to involve impaired serotonin and norepinephrine transmission in critical areas of the brain, most notably the frontal lobes. Like other complex psychiatric conditions, the etiology of depression seems to be multifactorial, with a strong genetic and psychosocial/environmental basis. The genetic basis of depression is suggested by statistics that indicate, for instance, that 25% of children who commit suicide have a family member or close relative who has committed suicide. Similarly, a family history of major depression is a significant risk factor for depression in children and adolescents. Studies suggest the incomplete penetrance of a dominant gene as a possible etiology for this finding. Regardless of the exact mechanism, genetic influences can increase the adolescent's vulnerability for depression. Specific environmental events can occur in an adolescent's life that may precipitate a depressive episode, such as the loss of a loved one or parental divorce. Other events, such as physical or sexual abuse, also can trigger depression in a susceptible teenager.

Differential Diagnosis

The differential diagnosis of depression includes any condition that may alter an individual's cognition or affect. For example, if a disease alters one's nutritional status and leads to malnourishment, this may alter affect and energy, which may resemble depression (Box 66.3). Examples of such diseases include cancer, tuberculosis, and eating disorders (eg, anorexia nervosa). Endocrine disorders, such as hypothyroidism, hyperthyroidism, and Addison disease, can mimic depression. Central nervous system (CNS) pathology, although rare, includes tumors, infections, postconcussion syndromes, and cerebrovascular accidents. Concomitant systemic illnesses, such as systemic lupus erythematosus, diabetes mellitus, and AIDS, can have CNS manifestations that may be mistaken for an isolated episode of depression. Although these diseases can occur, their prevalence pales in comparison to the prevalence and significant contribution of substance and alcohol abuse. It is also important to recognize that many chronic conditions are stressful and can place patients at risk for comorbid depression. Other mental

Box 66.3. Diagnosis of Depression in Adolescents

SIGE CAPS Mnemonic

S: Sleep changes
I: Interests—decreased interest in school or activities
G: Guilt, helpless, hopeless
E: Energy (decreased), fatigue
C: Concentration decreased
A: Appetite (increased or decreased)
P: Psychomotor agitation and retardation
S: Suicidal ideation

Criteria for Major Depressive Disorder

- Depressed or irritable mood most of the day, nearly every day
- Decreased interest in most daily activities, including school
- Significant weight changes
- Sleep problems (insomnia or hypersomnia)
- Psychomotor agitation or retardation
- Low energy or fatigue
- Feelings of worthlessness or guilt
- Diminished ability to concentrate or think
- Preoccupation with death or suicide

health conditions, such as early-onset bipolar disorder, can present initially with depressive symptoms. Approximately 20% to 40% of children with MDD eventually develop bipolar disorder. In contrast, longitudinal studies have found that very few individuals diagnosed with bipolar disorder as children meet criteria for the condition as adults. Another disorder to consider in children with depressive symptoms is disruptive mood dysregulation disorder, which was introduced in 2013 to identify those children with irritability and persistent, prolonged tantrums. Additionally, children with autism spectrum disorder often develop comorbid depression during adolescence as a manifestation of their isolation and poor coping skills. Other *DSM-5* psychiatric diagnoses to consider include adjustment disorders, uncomplicated bereavement, separation anxiety, and dysthymia, which is more chronic and sometimes less severe than major depression. Finally, side effects of prescribed and over-the-counter medications may produce clinical symptoms consistent with depression and therefore should be considered in the differential diagnosis.

Evaluation

History

The assessment of an adolescent for depressive symptoms is an important part of any routine encounter. At all visits a standardized screening tool should be given to the patient to complete before seeing the medical professional. These are short, quick assessments that provide an additional means by which a teenager can communicate depression or suicidality to the health professional before the start of the in-person encounter. Two such validated questionnaires are the Patient Health Questionnaire-9 (PHQ-9), which is a self-report survey with 9 questions based on *DSM-5,* and the *Columbia-Suicide Severity Rating Scale*. The PHQ-9 is composed of 9 questions with a score that ranges from 0 to 27. A score of 5 to 9 corresponds with mild depression, 10 to 14 with moderate depression, 15 to 19 with moderately severe depression, and 20 and above with severe depression. A positive result on either the PHQ-9 or the *Columbia-Suicide Severity Rating Scale* warrants a more comprehensive and complete conversation, especially if the screening tool for suicidality raises concern based on the validated scoring criteria.

A diagnosis of depression may be difficult to make after just 1 interview. At the initial visit, along with use of a depression/suicide screening tool, a complete psychosocial or HEADSS assessment (home, employment and education, activities, drugs, sexuality [including a history of sexual abuse or assault], suicide/depression) should be performed on all adolescents (see Chapter 4). The parent(s) or guardian(s) should be included during the first part of the interview to review their observations and concerns about their adolescent's behavior and mood, after which the teenager should be interviewed alone and a thorough history of recent feelings, behaviors, and attitudes should be obtained (Box 66.4). Mood changes should be noted; a labile affect can be a symptom of ongoing depression. The physician should keep in mind that malnourishment can result in a depressed or seemingly flat affect.

Box 66.4. What to Ask

History of Depression in an Adolescent

- Does the adolescent occasionally feel sad or "blue" and not understand why?
- Does the adolescent have unexplained crying spells?
- Does the adolescent feel "mad," "bored," or "grouchy"?
- Does the adolescent seem inappropriately jovial?
- Have any recent losses occurred in the adolescent's life that may explain his, her, or their feelings?
- Is the adolescent having trouble with concentration or memory?
- Does the adolescent have trouble falling asleep at night or have early morning awaking?
- Has the adolescent lost weight recently or shown any disinterest in food?
- Does the adolescent have any self-harm (eg, cutting) behaviors?
- Does the adolescent have feelings of hopelessness and have any desire to cause self-harm? Has the adolescent made any previous suicide attempts?
- Do the parents or siblings have a history of drug or alcohol use?
- Is there a family history of affective disorders? What has been their response to treatment?
- Is there a history of family violence?

A full psychiatric assessment also should be completed to obtain information about a possible comorbid condition, including features of psychosis, anxiety disorders, disruptive behaviors, and mania. It is important to note, however, that severe depression may be accompanied by symptoms of psychosis. Information about a family history of psychiatric illness or substance abuse, including alcohol abuse, also should be reviewed with the teenager as well as the parent(s) or guardian(s).

To identify youth at risk for suicide, health professionals must inquire about specific areas of adolescents' lives. Questions should be posed in an open and direct manner, such as, "Sometimes when people are very sad or upset they think of hurting themselves. Have you ever felt this way?", not, "You don't want to hurt yourself, right?" The health professional also should probe for a history of or ongoing sexual or physical abuse, assault, violence, or neglect as well as current interpersonal conflicts, such as fights, punishments, breakups, or traumas. An early history of sexual abuse has a strong association with the manifestation of suicidal ideation by age 15 years. Feelings of hopelessness, agitation, and impulsivity should be identified, along with frequent thoughts of suicide or death. It has been reported that having frequent thoughts of suicide is the best predictor of suicide attempts. Use of any illicit substance also raises the risk for suicide attempts. The adolescent who is suspected of being at risk for suicide must be questioned directly about suicidal ideation, specifically whether the teenager has a plan in mind and access to firearms, medications, or other means of suicide. Previous suicide attempts also must be reviewed with the teenager, because 35% to 45% of adolescents who complete suicide have a positive history of a previous attempt. Nonlethal suicide gestures or other methods

of self-inflicted harm should never be taken lightly or minimized. Initial questions should be nonspecific and become more specific as the interview proceeds, especially if answers to previous questions are positive (Box 66.5).

Promises to maintain confidentiality with the depressed adolescent who is considered at risk for suicide are discouraged because parental or guardian involvement is strongly advised. Precipitating and motivating factors for any previous suicide attempts should be determined before a treatment plan is developed. More important, the lethality of previous attempts must be evaluated.

Physical Examination

A thorough physical examination and review of systems should be completed to rule out a chronic medical condition, such as hypothyroidism, inflammatory bowel disease, lupus, or anemia, or an organic etiology for nonspecific symptoms. For the patient with a history of sexual abuse or assault or of sexual activity, a genital examination should be performed to evaluate for sexually transmitted infections, taking great care to avoid further trauma to the patient. In most cases, the physical examination may be of little yield in the adolescent with a true affective disorder; however, careful examination may reveal findings such as cut marks, track marks, skin picking, or loss of tooth enamel, any of which may be helpful in diagnosing a comorbid condition, such as substance abuse or an eating disorder. A careful detailed neurologic examination, including a mental status examination evaluating eye contact, rate of speech, spontaneity in conversation, thought content, affect, and processing, is essential in differentiating various psychiatric conditions (eg, bipolar disorder, schizophrenia).

Box 66.5. What to Ask

History of Risk for Suicide in the Adolescent

- Is the adolescent on any prescribed medications (eg, isotretinoin)?
- Is the adolescent experiencing any psychiatric difficulties, social maladjustments, or family or environmental challenges (eg, recent parental divorce or separation, school expulsion)?
- Does the adolescent have a history of symptoms of depression, conduct problems, or psychosis?
- How is the adolescent progressing in school?
- Does the adolescent have a history of substance abuse?
- Does the adolescent have any legal problems?
- Does the adolescent suffer any social isolation or have interpersonal conflicts with family or friends?
- Has the adolescent suffered any personal losses recently?
- Has a suicide recently occurred in the school or community?
- Are there any family problems, such as abuse or neglect?
- Has the adolescent ever thought that life was not worth living?
- Does the adolescent ever feel hopeless?
- Has the adolescent ever thought of causing self-harm?
- Does the adolescent have a previous history of suicide attempts?
- Does the adolescent currently have a plan for suicide?
- Does the adolescent have access to firearms, medications, or other means of suicide?

Laboratory Tests

Although no routine laboratory studies are regularly recommended, several laboratory tests warrant consideration in evaluating for physiologic contributions to depression. Such tests include a thyroid panel, fasting blood glucose level, complete blood count, electrolyte test, and urine or serum toxicology screening. Laboratory studies are also important screening measures prior to pharmacotherapy; thus, in addition to the aforementioned tests, the physician also should consider a blood urea nitrogen and creatinine test, liver panel, electrocardiography, and, in females, a pregnancy test. Psychometric testing may help rule out a concomitant learning disability or attention-deficit/hyperactivity disorder.

Imaging Studies

Radiologic imaging, such as computed tomography of the head or magnetic resonance imaging of the brain, is indicated if either the history or the physical examination is suggestive of a CNS process.

Management

Depression

Management of depression typically consists of psychotherapy, pharmacotherapy, or a combination of both. The National Institute of Mental Health supports psychotherapeutic intervention for mild depression. The types of therapy shown to be most effective for adolescents with depression include cognitive behavioral therapy and interpersonal therapy. For more severe depression or depression with suicidal ideation, the current first-line medical treatment in the primary care setting involves the use of selective serotonin reuptake inhibitors (SSRIs). Pharmacotherapy may be used with the aforementioned psychotherapies. Not all therapists are trained in the delivery of these therapeutic methods, however, and in many communities these interventions are not readily available. When psychotherapy is not available or is not effective, SSRIs may be necessary.

If depressive symptoms are associated with a specific adjustment disorder, such as divorce, a recent move, or death, and if family, peers, or school factors are affected, supportive counseling is indicated. The duration and depth of counseling depends, in part, on the comfort level of the primary care physician performing this task and how receptive the adolescent and family are to this intervention. Identification of the specific problem, exploration of the teenager's response to the problem, and development of a reasonable solution with the adolescent and parent(s) or guardian(s) may be helpful to improve adherence to psychotherapy. Regardless of the existence of a clear trigger for a depressive episode, medication may still be necessary when the symptoms impair daily functioning.

If family difficulties or dysfunction is the major issue, the family, adolescent, and physician or counselor should meet to assess the magnitude of the problem and the motivation required to address it. The physician should use this opportunity to educate the adolescent and the family about the signs and symptoms of depression and

the significant effect of depression on school functioning, family and peer relationships, and social interactions. Cognitive behavioral therapy is a specific type of therapy that has been found to be particularly helpful in adolescents with depression. The need for individual cognitive-behavioral or family therapy should be discussed as well as the effectiveness of psychiatric medication in the appropriate setting. Attention to parental mental health and understanding the strategies necessary to manage the adolescent's irritability and isolation also are extremely important. Psychological referral should be initiated if the patient requires more prolonged or intensive psychotherapeutic treatment, the severity of depression seems to worsen, suicidal behavior becomes an issue and additional mental health consultation is necessary, or a comorbid psychiatric condition is suspected.

Immediate psychiatric consultation and referral are indicated if an adolescent has severe depressive features that interfere with daily functioning or if the patient is experiencing suicidal intent, homicidal intent, or psychosis. Ensuring the adolescent's safety is the priority. A mental health referral is also appropriate if supportive counseling by the primary care physician has been ineffective or in cases of recurrent or chronic depression.

Psychiatric intervention generally includes pharmacotherapy in conjunction with psychotherapy, because most cases of depression include psychological, social, and environmental components. Although much attention has been given to safety concerns about the use of antidepressant medications among children and adolescents, SSRIs are considered first-line medications for the management of moderate to severe depression in teenagers. Two SSRIs, fluoxetine hydrochloride (eg, Prozac, Sarafem) and escitalopram oxalate (eg, Lexapro), have been approved by the US Food and Drug Administration (FDA) for managing depression in adolescents, but several other antidepressants are commonly prescribed in an off-label manner. Side effects of this class of medication tend to be dose related, and most subside with time (1–2 weeks) or with dose reduction. Common adverse effects include headache, abdominal pain, diarrhea, sleep changes, and jitteriness or agitation. Serious behavioral symptoms, such as aggression, hostility, and impulsivity, must be reviewed with a psychiatrist.

In 2004, the FDA added a black box warning for antidepressant medications stating that on rare occasions children and adolescents treated with these drugs have an increased likelihood for displaying suicidal behavior; however, no increase in the risk of completed suicides was noted in a meta-analysis conducted by the FDA. Subsequently, physicians wrote fewer prescriptions for antidepressants, which resulted in an increased rate of completed suicides. It now is generally accepted that although a small risk of suicidal behavior may exist, as long as patients are appropriately monitored the benefits of prescribing antidepressants outweigh the risks. This caution should be presented in context with the risks of untreated depression and discussed openly with the parent or guardian and the adolescent. Before starting the medication, informed consent must be obtained from the parent or guardian and assent must be attained from the teenager. Patients should be observed closely for worsening of symptoms, suicidal behavior, or unusual changes in behavior. Families should be educated on the importance of close follow-up and immediate, open communication with the physician should these symptoms occur. Initially, the adolescent should be seen or the family contacted frequently during the first 6 weeks of such treatment. Improvements in vegetative functions, such as sleeping and eating, often occur within the first 3 weeks. Family observations are initially more telling than self-observation. Often, the last feature to improve is the patient's self-report of mood elevation. An adequate trial of SSRIs is reported to be at least 4 to 6 weeks. Frequent medication adjustments are not advised, and abruptly stopping SSRIs is not recommended because of the possibility for a withdrawal syndrome. Stopping medication after several weeks should include a slow taper.

Suicide and Suicidal Behavior

Adolescents who are considered at risk for suicide must be asked directly at every visit if they are suicidal and if they have a plan (Box 66.5). Past suicide attempts are the most robust predictor of a future suicide attempt. Inquiry should include probes for thoughts of death, suicidal ideation, plan for suicide, means available, and intent. The teenager should be interviewed alone in an empathic and open-ended fashion. The parent or guardian also should be interviewed separately. Positive responses to this inquiry determine whether the adolescent will be treated on an inpatient or outpatient basis. The health professional should assess for protective factors as well (Box 66.6).

A suicide risk assessment and triage resource should be used, such as the SAFE-T suicide risk assessment (Table 66.1). In most cases, the adolescent with no previous suicide attempts, who exhibits ambivalence about suicidal thoughts, with no real intent to die, and with a good family support system may be treated as an outpatient. A safety plan must be devised, however. The patient is asked to agree to contact the clinician, parent, or another responsible adult if the patient feels a suicidal urge or experiences suicidal intent. The precipitants for possible suicidal behavior must be reviewed, and alternative methods for coping should be rehearsed with the teenager. Additionally, all potential means of suicide, particularly firearms and toxic medications, must be removed from the home or place of residence. It is not enough to "secure" firearms; they must

Box 66.6. Protective Factors

- Intact reality testing
- Children in home
- Spiritual beliefs and/or practices
- Moral beliefs
- Social stigma
- Future-oriented thought
- Presence of positive social relationships
- Fear of death and/or suicide
- Problem-solving skills
- Goals and/or aspirations

Table 66.1. Suicide Threat Assessment

Risk Level	*Risk/Protective Factor*	*Suicidality*	*Possible Interventions*
High	Psychiatric disorders with severe symptoms, or acute precipitating event; protective factors not relevant	Potentially lethal suicide attempt or persistent ideation with strong intent or suicide rehearsal	Admission generally indicated unless a significant change reduces risk. Suicide precautions
Moderate	Multiple risk factors, few protective factors	Suicidal ideation with plan, but no intent or behavior	Admission may be necessary depending on risk factors. Develop crisis plan. Give emergency/crisis numbers
Low	Modifiable risk factors, strong protective factors	Thoughts of death, no plan, intent or behavior	Outpatient referral, symptom reduction. Give emergency/crisis numbers

Reprinted with permission from Substance Abuse and Mental Health Services Administration. Suicide Assessment Five-step Evaluation and Triage (SAFE-T). Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009. www.integration.samhsa.gov/images/res/SAFE_T.pdf

be removed. Increased supervision must be implemented by parents or guardian as well as peers. Random room checks must be agreed on as well as an open-door policy until the therapist clears the patient for more privacy. The family also must agree to find a therapist and begin treatment immediately. An emergency plan must be developed, including "permission" to call 911. Resources should be provided. A crisis prevention card might be created that includes items such as identification of common triggers, an outline of coping skills, identification of a support system complete with telephone numbers, and the therapist's telephone number as well as a suicide hotline telephone number. Referral to a therapist is recommended as soon as possible. Preferably, this should be arranged while the adolescent is in the office, and the patient should be given a definite time and date for the appointment. Ideally, the therapist should meet with the family before the first appointment with the adolescent alone. Detoxification from drugs or alcohol, if necessary, also should be addressed with the family and teenager.

Because all suicidal threats, gestures, or ideations by adolescents must be taken seriously, emergent psychiatric referral is required for most of these individuals. The adolescent deemed to be at serious risk for suicide should be treated as an inpatient and admitted to a pediatric or adolescent unit for 72 hours of observation. The purpose of this brief hospitalization is 3-fold: to stabilize the patient medically, if necessary; to observe and evaluate patient-family dynamics; and to impress on the patient and family that the attempt has been recognized and taken seriously. Intervention requires the involvement of mental health professionals and social services. Referral to the emergency department for any patient considered to be of moderate to severe risk or anyone who concerns the health professional is crucial. It is not the role of the primary care physician to clear someone of the need for emergent psychiatric intervention.

Prognosis

The risk of recurrence of major depression in adolescents who have recovered is substantial. One study reports that 5% of patients relapse within 6 months of recovery, 12% within 1 year, and an estimated 33% within 4 years. Higher rates of recurrence have been reported, however, with approximately 70% of teenagers with MDD experiencing another depressive episode within 5 years. Additionally, youth with a depressive disorder have a 4-fold risk for experiencing the same disorder as an adult. Prepubertal-onset depression is associated with an approximately 30% risk for future bipolar disorder or mania.

The risk of repeated suicidal behavior seems to be greatest within the first 3 months after the initial attempt. Reported reattempt rates are 6% to 15% in the first 1 to 3 years after the initial attempt.

CASE RESOLUTION

The girl's symptoms may be indicative of depression, because she has a flat affect and seems to be somewhat isolated (ie, insufficient time for friends, recent move to the United States). After much inquiry, she seems to be at low risk for suicide; however, her PHQ-9 score of 11 indicates that she is at moderate risk of depression. The physician should continue to inquire about symptoms of depression and ask her directly about suicidal behaviors, then arrange for cognitive behavioral therapy and close follow up. If depression is confirmed and does not improve with therapy, medication may be indicated. If the girl becomes suicidal, she and her family should be referred to an emergency department for an emergent mental health evaluation and possible intervention, including hospital admission.

Resources

Columbia-Suicide Severity Rating Scale
http://cssrs.columbia.edu

Military OneSource
www.militaryonesource.mil

National Suicide Prevention Lifeline
800-273-TALK (8255)

Safety Planning Intervention
www.suicidesafetyplan.com

Substance Abuse and Mental Health Services Administration (SAMHSA)
www.samhsa.gov

Garrett Lee Smith State/Tribal Youth Suicide Prevention Program and Early Intervention Grant Program
www.samhsa.gov/grants/grant-announcements/sm-19-006

Suicide Prevention Resource Center
www.sprc.org

American Indian and Alaska Native suicide prevention programs
www.sprc.org/settings/aian

CALM: Counseling on Access to Lethal Means
www.sprc.org/resources-programs/calm-counseling-access-lethal-means

Safety Planning Guide: A Quick Guide for Clinicians
www.sprc.org/sites/default/files/SafetyPlanningGuide%20Quick%20Guide%20for%20Clinicians.pdf

Zero Suicide in Health and Behavioral Health Care
zerosuicide.sprc.org

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PART 5

Acute and Emergent Problems

CHAPTER 67

Fever and Bacteremia

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CASE STUDY

An 8-month-old girl is brought to the emergency department with a 2-day history of fever and increased fussiness. She is irritable but consolable by her parents. Her parents believe that her immunizations are current, but they do not have the immunization record with them. On examination, she has a rectal temperature of 39.5°C (103.1°F). The rest of the physical examination is within normal limits, and no source for the fever is apparent.

Questions

1. What are the serious bacterial infections in febrile newborns and infants?
2. What has been the effect of conjugated vaccines against *Haemophilus influenzae* and *Streptococcus pneumoniae* on the incidence of bacteremia and meningitis in febrile newborns and infants?
3. What are the challenges in differentiating between serious and benign febrile illnesses in young children?
4. What diagnostic studies are recommended in the evaluation of febrile newborns, infants, and children?
5. When are empiric antibiotics indicated, and when should febrile newborns and infants be hospitalized?

Fever is among the most common chief complaints among pediatric patients seeking medical attention in physician offices, urgent care centers, and emergency departments and accounts for up to 30% of these visits. Most such patients have a benign, self-limited viral illness. Some patients, however, have a serious bacterial infection (SBI), such as meningitis, urinary tract infection (UTI) and/or pyelonephritis, pneumonia, bacteremia, septic arthritis, osteomyelitis, cellulitis, or deep tissue infection. *Bacteremia* is a bacterial infection within the bloodstream; it is considered occult in the absence of an apparent source of infection after a thorough physical examination in an otherwise healthy-appearing child.

Epidemiology

Historically, management decisions about febrile children have been largely dictated by age. Patients are typically divided into the following age-defined categories: newborns and infants younger than 90 days, infants and young children 3 to 36 months of age, and children age 3 years and older. Febrile newborns and young infants (ie, younger than 90 days) have higher rates of SBI than older children and often represent a diagnostic challenge. They have relatively immature immune systems, which renders them particularly susceptible to bacterial infections and have not yet received most of their immunizations. They often have limited responses to bacterial infections and exhibit relatively nonspecific signs and symptoms. In addition, newborns and young infants have different bacterial pathogens that can cause these serious infections, including *Escherichia coli*; *Streptococcus agalactiae* (group B streptococci); less commonly, *Streptococcus pneumoniae*; and, rarely, *Listeria monocytogenes* and other gram-negative organisms (Box 67.1). The overall prevalence of SBI among febrile newborns and infants younger than 90 days with a temperature of 38.0°C (100.4°F) or higher is approximately 10%; the rate approaches 20% in newborns younger than 28 days. Urinary tract infections are by far the most common source of SBI, with a smaller percentage having pneumonia, bacteremia, or meningitis. Contemporary studies have demonstrated that febrile newborns and young infants with diagnosed viral infections have lower rates of SBI than those without viral infections (4% and 12%, respectively). In these studies, none of the febrile newborns and young infants with viral infections confirmed on diagnostic testing had meningitis, but some did have UTIs and, rarely, bacteremia.

Febrile infants and children age 3 to 36 months are at a higher risk for bacteremia than older children but less so than newborns and young infants. Although the physical examination is more reliable in this age group than in newborns and younger infants, in many patients the examination is normal without any localizing source of infection. These individuals may, in turn, have occult bacteremia. Vaccine development and widespread immunization programs have dramatically changed the epidemiology and clinical course of bacteremia in this age group within the United States over the past several decades. Before the introduction of the *Haemophilus influenzae* type b (Hib) and pneumococcal vaccines, the prevalence rates of bacteremia were approximately 3%. During this time, *Haemophilus* was considered the most significant organism causing bacteremia because of its invasiveness and ability to cause localized infection, particularly meningitis. In the mid-1980s, the Hib vaccine was introduced, which has nearly eliminated this particularly invasive organism. In the post-Hib but prepneumococcal conjugate vaccine era, the rates of occult bacteremia ranged from 1.6% to 1.9% in children with a

Box 67.1. Organisms Implicated in Serious Bacterial Infection/Occult Bacteremia in Children

Newborns and Infants Age 3 Months and Younger

- *Escherichia coli*
- Group B streptococci
- *Streptococcus pneumoniae*
- *Listeria monocytogenes*
- *Salmonella* species (infants >1 month)
- *Haemophilus influenzae* type b (Hib[a]; infants >1 month)

Children Age 3–36 Months

- *S pneumoniae*
- *Neisseria meningitidis*
- *Salmonella* species
- *Staphylococcus aureus*
- Hib[a]

[a] Hib disease has been nearly eliminated with the routine use of Hib conjugate vaccines.

temperature of 39.0°C (102.2°F) or higher and no obvious source of infection. More than 90% of cases of occult bacteremia in this age group were caused by *S pneumoniae*, with the remainder being caused by *Salmonella, Neisseria meningitides, Staphylococcus aureus,* and a few other rare organisms. Pneumococcus is not as virulent a microorganism as some other bacteria, and many cases of occult pneumococcal bacteremia resolved spontaneously without any intervention. Left untreated, a small percentage (3%–5%) went on to develop pneumococcal meningitis, which has the most serious complication and fatality rate. In 2000, the heptavalent pneumococcal conjugate vaccine was licensed by the US Food and Drug Administration for use within the United States. This vaccine provided coverage against the 7 main serotypes of *S pneumoniae*, which were responsible for approximately 80% of the cases of invasive pneumococcal disease in the United States and Canada at the time. Following the introduction of this vaccine, the rate of invasive pneumococcal disease (including bacteremia) and carriage for the serotypes covered by the vaccine dropped considerably. Additionally, there was evidence suggestive of herd immunity, in that a decline in invasive pneumococcal disease was noted among older individuals who had not received the vaccine. Consequently, a selective pressure has increased the prevalence of invasive pneumococcal disease caused by strains not covered by the heptavalent vaccine, although the overall magnitude of this effect appears to be relatively small. Additionally, other bacteria, such as *E coli, Salmonella,* and *S aureus*, appear to have increased in relative frequency as a source of bacteremia. In 2010, a new 13-valent pneumococcal conjugate vaccine (PCV13) was licensed and expanded coverage to include 6 different serotypes that have emerged with increasing frequency as a cause of invasive pneumococcal disease following the introduction of the heptavalent vaccine. The American Academy of Pediatrics and the Advisory Committee on Immunization Practices currently recommends the pneumococcal conjugate vaccine (ie, PCV13) for all infants in a 4-dose regimen to be given at 2, 4, 6, and 12 to 15 months of age. A pneumococcal polysaccharide vaccine (PPSV23) was approved in late 2014 that provides even broader protection. The addition of PPSV23 is recommended for children older than 2 years with certain high-risk chronic medical conditions after they have received PCV13. Continued surveillance of invasive disease is necessary to ascertain what effect the changes in epidemiology of these newer vaccines may have on the diagnosis and management of bacteremia in young febrile children. Preliminary data have shown a 42% decrease overall in the incidence of invasive pneumococcal infection in 2011 after the implementation of routine PCV13 immunization and a 53% decrease in the incidence in children younger than 24 months compared with years 2007 through 2009.

Clinical Presentation

In many children, fever is the only symptom or manifestation of disease and no other signs or symptoms may be apparent. These children may look well and behave normally. Young children, especially newborns and infants younger than 3 months, are likely to have fewer and more subtle behavioral signs with bacterial infections. Physicians must, therefore, maintain a high index of suspicion for the presence of an SBI, even in the absence of localizing signs (Box 67.2). Occult bacteremia, by definition, has no abnormal physical manifestations aside from fever.

Pathophysiology

Fever is an elevation in the thermoregulatory set point of the body. The thermoregulatory center is located in the preoptic region of the anterior hypothalamus, and an elevation in the hypothalamic set point above the normal body temperature initiates the physiologic changes that result in fever. Exogenous pyrogens (eg, bacteria, viruses, antigen-antibody complexes) stimulate host inflammatory cells (eg, macrophages, polymorphonuclear cells) to produce endogenous pyrogens. Interleukin-1 is currently regarded as the prototypical endogenous pyrogen. Endogenous pyrogens cause the hypothalamic endothelium to increase intermediary substances, such as prostaglandins and neurotransmitters, which then act on the preoptic neurons of the anterior hypothalamus to produce an elevated set point. The body uses physiologic mechanisms (eg, peripheral vasoconstriction, shivering) and behavioral actions

Box 67.2. Diagnosis of Serious Bacterial Illness in Children

- Lethargy, irritability, or change in mental status
- Tachycardia disproportionate to the degree of temperature elevation
- Tachypnea or labored respirations
- Bulging or depressed anterior fontanel
- Nuchal rigidity
- Petechiae
- Localized erythema, tenderness, or swelling
- Abdominal or flank tenderness
- Fever

(eg, bundling up, drinking hot tea) to increase body temperature to reach and maintain this higher set point, thus producing fever (Figure 67.1).

This contrasts with hyperthermia, in which the thermoregulatory set point of the body is normal. Because of abnormal physiologic processes, heat gain exceeds heat loss, and the body temperature rises despite efforts to return to the control set point.

Differential Diagnosis

In most cases, the duration of fever in children is short, and signs and symptoms are localized. Fever without a source involves an acute episode of fever that lasts 1 week or less in children in whom history, physical examination, and laboratory tests do not reveal a source. Most affected children are eventually diagnosed with an acute, generally benign, infectious illness. Occult bacteremia remains a major concern in young children, primarily in infants younger than 3 months. High-risk factors for occult bacteremia are presented in Box 67.3. *Fever of unknown origin* is fever of at least 8 days' duration in infants or children in whom routine history, physical examination, and laboratory assessment do not reveal a source.

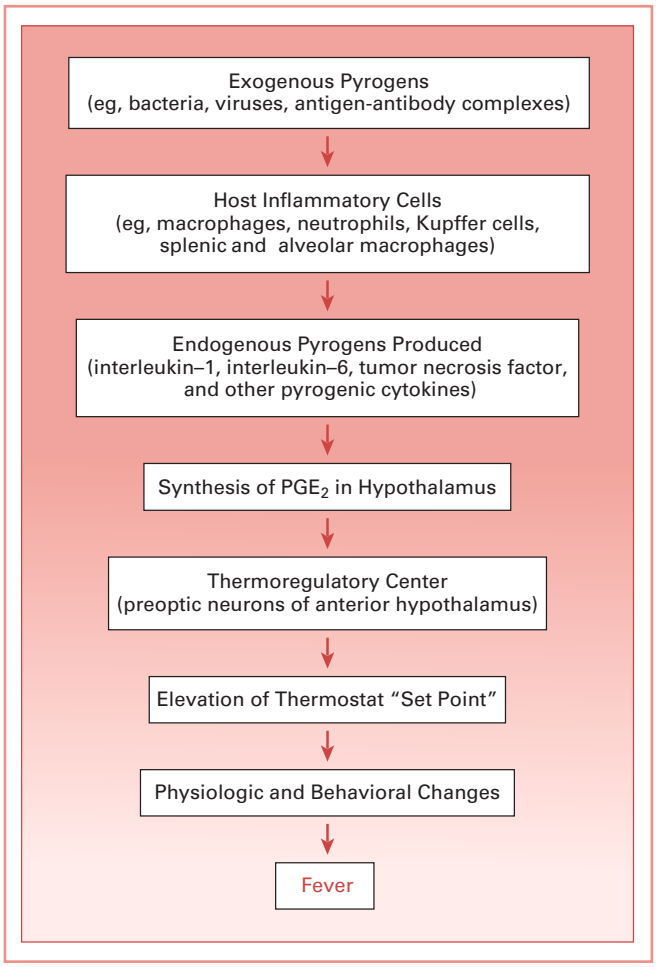

Figure 67.1. Pathophysiology of fever production. Antipyretic agents work by blocking the synthesis of prostaglandin E_2 (PGE_2).

The differential diagnosis of children with an acute febrile illness is primarily infectious (Box 67.4), including benign and generally self-limited illnesses (eg, upper respiratory infections) and less common but more serious illnesses (eg, meningitis, osteomyelitis). Occasionally, a child with a fever without a source has a

Box 67.3. Risk Factors for Occult Bacteremia

- Age 36 months or younger
- Temperature ≥39.5°C (≥103.1°F)
- White blood cell count ≥15,000 cells/mm^3 or ≤5,000 cells/mm^3
- Total band cells ≥1,500 cells/mm^3
- Erythrocyte sedimentation rate ≥30 mm/hour
- Underlying chronic disease (eg, malignancy, immunodeficiency, sickle cell disease, malnutrition)
- Clinical appearance (eg, irritability, lethargy, toxic appearance)

Box 67.4. Common Infectious Causes of an Acute Episode of Fever in Children

Upper Respiratory Tract
- Upper respiratory infection (ie, common cold)
- Otitis media
- Sinusitis

Pulmonary
- Bronchiolitis
- Pneumonia

Oral Cavity
- Gingivostomatitis
- Pharyngitis
- Dental abscess

Gastrointestinal Tract
- Acute gastroenteritis (bacterial or viral)
- Appendicitis

Genitourinary Tract
- Urinary tract infection
- Pyelonephritis

Musculoskeletal
- Septic arthritis
- Osteomyelitis

Central Nervous System
- Meningitis
- Encephalitis

Miscellaneous (Including Noninfectious Causes)
- Bacteremia
- Immunization reaction
- Viral exanthems (eg, chickenpox, measles)
- Neoplasia
- Collagen vascular disease

noninfectious illness, such as collagen vascular disease or neoplasia. By comparison, the differential diagnosis of children with fever of unknown origin is quite broad and includes infectious and noninfectious disorders (Box 67.5).

Evaluation

History

The medical history provides a great deal of valuable information in the evaluation of children with fever (Box 67.6). The history should focus on the duration and severity of the fever as well as the presence of associated symptoms that may localize an infection to a specific organ system. Additionally, caregivers should be specifically asked about infectious risk factors, such as potential sick contacts, immunization status, and chronic medical conditions.

Box 67.5. Common Causes of Fever of Unknown Origin in Children

Infectious Diseases

Bacterial
- Localized infection: mastoiditis, sinusitis, pneumonia, osteomyelitis, pyelonephritis, abscess (eg, abdominal, pelvic)
- Systemic: tuberculosis, brucellosis, salmonellosis, leptospirosis, tularemia

Viral
- Hepatitis viruses
- Cytomegalovirus
- Epstein-Barr virus (infectious mononucleosis)
- HIV

Fungal
- Disseminated coccidioidomycosis
- Disseminated histoplasmosis

Miscellaneous
- Malaria
- Rocky Mountain spotted fever
- Syphilis
- Lyme disease

Neoplasia
- Leukemia
- Lymphoma
- Hodgkin disease
- Neuroblastoma

Collagen Vascular Diseases
- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Rheumatic fever

Miscellaneous
- Inflammatory bowel diseases
- Kawasaki disease
- Thyroiditis
- Drugs
- Factitious fever

Box 67.6. What to Ask

Fever and Bacteremia
- How long has the child had fever? How high has the temperature been?
- Does the child have any other symptoms, such as rash, vomiting, diarrhea, abdominal pain, or dysuria; cough, rhinorrhea, or other respiratory symptoms; lethargy, irritability, or change in mental status?
- Is anyone sick at home?
- Has the child's activity level changed (eg, more sleepy than usual), or is the child more irritable than usual?
- What immunizations has the child received?
- Is the child taking any medications?
- Do any pets live in the house?
- Has there been any history of recent travel, especially outside the country?
- Has the child ever been hospitalized for an infectious illness?
- Does the child have any medical problems, especially asthma, sickle cell anemia, congenital heart disease, or immunodeficiency?

Physical Examination

Rectal temperature should be obtained in all newborns, infants, and young children. Temperatures obtained by other routes (eg, axillary, oral, cutaneous) are less reliable. An elevation in rectal temperature in a newborn or an infant should not be attributed to overbundling. Other vital signs may also provide important diagnostic clues. Tachycardia disproportionate to the degree of temperature elevation may be suggestive of dehydration or sepsis. Tachypnea may be the only sign of a respiratory infection, and it also can occur in response to metabolic acidosis (eg, secondary to sepsis or shock). These changes may suggest an occult focus of infection. Response of the temperature and other vital signs to antipyretic agents should be noted; the physician must remain cautious, however, because a clinical improvement in response to antipyretic agents can occur even in the setting of an SBI. Newborns and young infants with recorded fevers at home but who are afebrile on physician evaluation should be treated as if they have a fever. The report of a tactile fever without a recorded temperature is sensitive, but not specific, and therefore overestimates the true likelihood of a fever. In newborns and young infants in whom the risk of SBI is relatively high, however, the report of a tactile temperature should be taken seriously, and these patients should be managed as though the fever were documented.

Observation of the overall hydration status and activity of the patient is extremely important. An attempt should be made to determine whether the patient is behaving and responding in an age-appropriate fashion. Physicians should look for eye contact,

spontaneous motor movements, negative responses to adverse stimuli, and positive responses to pleasant stimuli.

All febrile children should undergo a complete physical examination. This is important even when the history may suggest involvement of only 1 organ system. For example, in young children vomiting and fever may be signs of a viral illness, but they also may signal a more serious infection such as a UTI or meningitis. The underlying condition may go undiagnosed unless a thorough examination and appropriate diagnostic evaluation are performed.

The anterior fontanel should be palpated. It may be normal, bulging as a result of CNS infection, or depressed secondary to dehydration. The ears should be examined carefully and pneumatic otoscopy performed to evaluate for otitis media as the source of fever, especially in children younger than 3 years. The occurrence of otitis media should not preclude further workup for invasive bacterial disease in children who do not appear well (see Chapter 87). The oropharynx also should be examined. Dry mucous membranes may indicate dehydration. Enlarged, inflamed, or exudative tonsils may signal the presence of a viral infection or group A streptococcal infection in older children. Respiratory symptoms, such as retractions, nasal flaring, grunting, stridor, rales, rhonchi, and wheezing, may all be clues to respiratory tract infections. Enanthems on the buccal mucosa or exanthems on the skin are often signs of viral infections. The presence of petechiae in association with fever is usually benign; in rare cases, however, it may indicate a serious underlying infection, such as meningococcemia. The capillary refill time, quality of peripheral pulses, and the general temperature of the extremities can be used to assess perfusion. Localized areas of tenderness, erythema, swelling, induration, or fluctuation may point to cellulitis, septic arthritis, osteomyelitis, or the presence of an abscess. Nuchal rigidity can be an important clue to the presence of meningitis. This clinical finding is rarely present in children younger than 15 to 18 months, and physicians must rely on other clinical factors and maintain an index of suspicion for meningitis in febrile children of this age. Newborns and infants with meningitis may display paradoxical irritability, which is when crying is made worse by holding and trying to console the child.

Laboratory Tests

Newborns and Infants 90 Days or Younger

The physical examination alone cannot reliably identify an SBI in newborns and infants 90 days or younger. For all patients with a temperature of 38.0°C (100.4°F) or higher, a thorough evaluation for a bacterial source of infection is therefore required. This evaluation includes a complete blood cell count (CBC) with differential, urinalysis with microscopic evaluation, and blood and urine cultures. Cerebrospinal fluid studies and cultures should be performed on all newborns and infants younger than 29 days and strongly considered for those aged between 29 to 90 days. Peripheral white blood cell (WBC) counts, although possibly helpful in older infants and children, do not reliably predict UTIs, bacteremia, or meningitis in febrile newborns and young infants. Decisions about whether to send blood and urine cultures or to perform a lumbar puncture should not be based on the screening peripheral WBC count in this age group. Additionally, the standard urinalysis has a sensitivity of only approximately 85% in this age group and should not be used to determine the need for urine culture.

Rapid viral diagnostic techniques that can reliably identify several of the more common viral pathogens (eg, respiratory syncytial virus, influenza, adenovirus, parainfluenza) are becoming increasingly available. The presence of a positive viral test result, however, does not automatically preclude further diagnostic testing in this age group. Studies have identified a small but significant number of patients with UTIs who also happen to have a positive viral test result, and for this reason, urine culture should still be routinely obtained. The risk of bacteremia and meningitis is significantly decreased, however, and in well-appearing patients older than 1 month with a positive viral test result further testing may not be indicated or cost effective.

If empiric antibiotics are to be administered, a lumbar puncture must be performed so as not to obscure the possibility of partially treated meningitis should pleocytosis be discovered on a subsequent cerebrospinal fluid specimen. Stool analysis and culture should be reserved for febrile newborns and young infants with diarrhea. Routine diagnostic radiographic studies (eg, chest) are not necessary and should be reserved for infants with respiratory symptoms or examination findings (eg, tachypnea, hypoxia, rales, wheezes, increased work of breathing).

Infants 3 to 36 Months of Age

The diagnostic approach to older infants and young children has changed following the introduction of pneumococcal conjugate vaccines. Before widespread vaccine use, the standard of care involved an aggressive diagnostic approach looking for occult bacteremia in febrile children 3 to 24 months of age with temperature higher than 39.0°C (102.2°F) and in febrile children 2 to 3 years of age with temperature higher than 39.5°C (103.1°F) without any apparent source of infection. This historical approach included a screening CBC, blood cultures, and empirically treating infants and children with an elevated WBC count greater than 15,000 cells/mm^3 or an absolute neutrophil count (ANC) greater than 10,000 cells/mm^3 because they were at higher risk for occult bacteremia. The ANC was generally considered to be the best predictor of risk for occult bacteremia. More recently, other acute phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and procalcitonin, have been studied. These levels are all commonly elevated in serious infections but have inadequate sensitivity and specificity and have not been shown to be reliably better predictors for occult bacteremia than the peripheral WBC count or ANC. At this time other laboratory tests, including antigen testing, serum cytokine measurements, and polymerase chain reaction (quantifying the patient's molecular response to infection), are not particularly useful because of their limited availability, relatively high false-positive rates, or cost. However, there is significant interest and ongoing study of these technologies and it is probable that they will be part of patient care in the future, but currently there is no single test that has reliably identified all young febrile children with occult bacteremia.

With the declining prevalence of invasive pneumococcal disease postlicensure of the heptavalent conjugate vaccine and the further decrease with PCV13, the need for routine screening, culturing, and selective antibiotic use for occult bacteremia has been challenged. The peripheral WBC count has become a less useful screening tool in an era of such low rates of invasive disease. Additionally, the rates of contaminated blood cultures are now much higher than actual cases of bacteremia, which often results in unnecessary additional testing, hospitalization, antibiotic administration, and family stress. *Infants and children who have received at least 2 doses of the PCV13 vaccine can be safely managed without blood tests, because this is no longer a cost-effective strategy.* Individuals who are at increased risk because they are unimmunized, whose vaccine status is uncertain, or who have received only 1 dose of the vaccine may need screening evaluation with CBC, blood, and urine cultures and expectant antibiotics if they are found to have an elevated WBC count or ANC. The increase in herd immunity and change in epidemiology of bacteremia following the widespread use of the pneumococcal vaccine may warrant reconsideration of this in the future following long-term surveillance of invasive disease.

Infants with temperature higher than 39.0°C (102.2°F) warrant urine testing, especially in girls younger than 2 years, uncircumcised boys younger than 12 months, and circumcised boys younger than 6 months. Chest radiography should be considered in infants with significant respiratory symptoms or auscultatory findings suggestive of pneumonia. In infants with temperatures higher than 39.5°C (103.1°F) and WBC counts greater than 20,000 cells/mm^3, chest radiographs should also be obtained to detect occult pneumonia, which is reported in up to 25% of these patients, even in the absence of significant respiratory symptoms or auscultatory findings.

Children Older Than 3 Years of Age

The laboratory evaluation of children older than 3 years is individualized and influenced by the history and physical examination; most patients do not need any testing. Healthy children in this age group are not at high risk for occult bacteremia. The physical examination of children this age is more reliable, and they are better able to communicate their symptoms than younger children. Routine screening tests are not generally indicated in healthy individuals and should be reserved for those who appear toxic or have an underlying disease that puts them at increased risk for bacterial infections (eg, sickle cell disease, cancer, immunodeficiency, nephrotic syndrome).

Imaging Studies

As noted previously, chest radiography is the most common imaging study done in the routine evaluation of a newborn, infant, or child with fever and symptoms consistent with lower respiratory infection or with fever and no apparent source. Other imaging studies, such as bone scanning, gallium scanning, magnetic resonance imaging, and computed tomography, are indicated if infection is suspected, such as an occult abscess or osteomyelitis, and if positive imaging findings will change patient management. Brain computed tomography is not needed prior to lumbar puncture in young children without focal neurologic deficits.

Management

Management of children with fever includes controlling the fever and managing the underlying process causing the fever. No evidence exists that fever itself is harmful. To the contrary, animal studies have suggested that fever may have some survival advantage. Despite the possible beneficial effects of fever, febrile children may feel uncomfortable, and fever should be reduced to relieve the associated discomfort and malaise. Antipyretic agents, such as acetaminophen and ibuprofen, can be used. The use of both of these medications concurrently can result in dosing errors; therefore, in most cases, families should be advised to use only a single medication. Aspirin should not be used for fever control in children because of the association with Reye syndrome and viral illnesses. Sponging or bathing with tepid water and unbundling children aid in fever reduction. Ice water or alcohol baths should be avoided to prevent inadvertent hypothermia.

All toxic-appearing febrile newborns, infants, and children, regardless of age, require hospitalization and administration of broad-spectrum antibiotics. Hospitalization and the initiation of empiric intravenous (IV) antibiotics are recommended for all febrile newborns 28 days or younger pending culture results. Ampicillin and gentamicin are the most commonly used initial antibiotics within this age group; however, use of these antibiotics must be considered carefully in the context of resistance patterns and local practice within a geographic region. With the onset of standard group-B streptococcus surveillance during pregnancy and the use of intrapartum antibiotics, more gram-negative organisms and increased gentamicin resistance have been reported, necessitating the use of a third-generation cephalosporin, such as cefotaxime, for initial empiric coverage. Ceftriaxone is generally avoided in this age group, particularly among jaundiced newborns, because of its ability to displace bilirubin from albumin, thereby increasing the risk of kernicterus. The addition of empiric vancomycin and/or acyclovir should be considered for patients at risk for resistant gram-positive organisms or congenital *Herpes simplex* infection.

Well-appearing febrile infants aged 29 to 90 days may be treated on an outpatient basis with antibiotics (ceftriaxone 50 mg/kg intravenously or intramuscularly) or close observation alone, provided they meet established low risk for SBI criteria (Box 67.7). For this approach to be safe, however, parents or guardians must be reliable and have means of communication and transportation in the event of a positive culture result so that they can be notified to return the infant for reevaluation and possible admission. All febrile infants aged 29 to 90 days need very close follow-up, typically within 24 hours. Most pathogens are isolated from cultures within the first 24 hours, and hospitalization with IV antibiotics is generally warranted for any young infant with a positive culture result consistent with a pathogen. The addition of vancomycin must be considered if resistant pneumococcus is a possibility.

The management of well-appearing febrile infants and children between 3 and 36 months of age is dependent on the identification of a focal infection on physical examination or diagnostic studies. Antibiotics should be administered if a bacterial infection is identified. Well-appearing infants who are tolerating oral fluids

Box 67.7. Low-Risk Criteria for Serious Bacterial Infection in Young Febrile Infants

1. Well-appearing
2. No focal bacterial infection apparent on examination
3. Previously healthy term infant with unremarkable neonatal course
4. WBC count between 5,000 and 15,000 cells/mm^3
5. Absolute band cell count <1,500 cells/mm^3 or a band-to-neutrophil ratio of ≤0.2
6. Normal cerebrospinal fluid examination with <8 WBCs per high-power field and negative Gram stain
7. Normal urinalysis with <10 WBCs per high-power field
8. Stool studies with <5 WBCs per high-power field (if diarrhea present)
9. Normal chest radiograph (if respiratory signs/symptoms present)

Abbreviation: WBC, white blood cell.

well and have no significant respiratory distress or hypoxia can be managed on an outpatient basis, even if they have a UTI or pneumonia. Clinicians may administer a dose of ceftriaxone for the first 24 hours and transition to an oral antibiotic thereafter. Continued close follow-up is necessary, usually within 24 to 48 hours. Infants who have received 1 dose or less of the pneumococcal vaccine can receive a dose of ceftriaxone pending culture results if the WBC count is greater than 15,000 cells/mm^3 or the ANC is greater than 10,000 cells/mm^3.

Healthy and well-appearing febrile children older than 3 years can be treated on an outpatient basis if they are well hydrated and have no respiratory distress or hypoxia. Children with underlying medical conditions or who are at risk for bacterial infections may require treatment in the hospital with IV antibiotics regardless of age, depending on their individual circumstances.

Children with occult pneumococcal bacteremia who are afebrile and well-appearing at follow-up likely can continue to be treated on an outpatient basis. Additional dosing of ceftriaxone may be necessary; transition to an oral antibiotic can be considered if sensitivity testing has been performed. Repeat blood cultures likely are not necessary if the child is afebrile, because the likelihood of persistent bacteremia is low. Those who are younger than 90 days, are still febrile at follow-up, or have clinically worsened warrant hospitalization and IV antibiotics. Additionally, a lumbar puncture should be considered if not previously performed in a child with a positive blood culture. All individuals with occult *N meningitides* bacteremia warrant hospitalization and IV antibiotics. A lumbar puncture also should be strongly considered if not previously performed because of the substantial risk for meningitis with this particular microorganism. In general, most other cases of occult bacteremia warrant hospitalization and IV antibiotics. Consultation with an infectious disease specialist may be indicated to determine appropriate antibiotic selection and duration of therapy.

Prognosis

Occult bacteremia may resolve without therapy and have no sequelae, but it may persist or produce localized infections, such as meningitis or septic arthritis. In children with bacteremia who do not undergo antimicrobial therapy, the risk of persistent bacteremia is approximately 20% and the risk of meningitis is approximately 5% to 10%. These risks vary depending on which organism is isolated from the blood. In general, the risk of developing serious sequelae is greater with bacteremia caused by *H influenzae* than *S pneumoniae* (25% and 5%, respectively). Currently, concern about SBI related to either of these organisms is significantly diminished with the introduction of the conjugate vaccines.

CASE RESOLUTION

The infant is irritable and has a high fever of unknown source. Her vaccine status is uncertain. No source of her infection is revealed on physical examination. Because her fever is 39.5°C (103.1°F), she is irritable, and her immune status is uncertain, a complete laboratory assessment, including a lumbar puncture, should be performed. Management should be determined after all laboratory data are available. If laboratory assessment reveals a focus of infection, such as a UTI, she should be managed with antibiotics. If laboratory assessment does not reveal a source for the fever and her WBC count is greater than 15,000 cells/mm^3 or her ANC is greater than 10,000 cells/mm^3, she can be administered an intramuscular injection of ceftriaxone as expectant management for occult bacteremia and undergo reevaluation in 24 hours or undergo treatment without antibiotics.

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CHAPTER 68

Emerging Infectious Diseases

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CASE STUDY

A previously healthy 8-year-old boy is brought to his pediatrician's office in late August with 2 days of fever, fatigue, headache, myalgias, nausea, and gingival bleeding. On the morning of the visit his mother noted a rash on his legs. He lives with his family in the Northeastern United States but recently returned from a 1-week vacation in Key West, Florida. He engaged in extensive outdoor activities, including snorkeling, hiking, and several evening boat trips, and he sustained multiple mosquito bites during the trip. He received all routine childhood immunizations, denies any allergies, and takes no medications. No other family members are ill.

On physical examination, his temperature is 38.7°C (101.7°F) and he is generally ill-appearing. He has photophobia and mild meningismus, and a petechial rash is noted on his trunk and lower extremities. Laboratory studies sent from the office reveal microscopic hematuria, leukopenia (white blood cell count 2,800 cells/mm^3), and thrombocytopenia (platelet count 85,000 platelets/mm^3).

Questions

1. What is an emerging or reemerging infection?
2. What pathogens are associated with emerging infections?
3. What are some common or emerging infectious diseases that may cause the clinical syndrome in the case scenario?
4. How does recent travel influence the differential diagnosis?
5. What resources can a primary care physician access to help in making a diagnosis?

Emerging and reemerging infectious diseases are defined as those for which the incidence in human populations has increased in the past 2 decades or threatens to do so in the near future. They may represent the resurgence of an ancient human scourge, a novel zoonosis that has broadened its host range, a common pathogen that has acquired a new antimicrobial resistance profile, or more rarely a previously unidentified or unknown microorganism. A startling diversity of organisms has met these criteria, including viral, bacterial, fungal, and parasitic pathogens. Likewise, a variety of factors affect the emergence or reemergence of these pathogens, including range and susceptibility of human hosts, evolution and antigenic shift of the pathogen, and ecological and environmental changes, such as vector amplification or breakdown of public health measures. Although a select few of these emerging pathogens represent malicious propagation or bioterrorism, most appear spontaneously at ambulatory or emergency health facilities and thus are relevant to the practicing primary care physician. It has only been through astute clinical observation, targeted outbreak investigation, and a coordinated public health response that many emerging infectious diseases have been identified.

In this chapter we review the factors involved in the emergence and reemergence of infectious diseases of public health significance, discuss several specific examples that are likely to be most relevant to pediatric practice, summarize regional and global outbreaks of emerging infectious diseases, and provide practical steps for the primary care physician to access local diagnostic and public health support.

Contributing Factors

The spectrum of infectious diseases has always changed and evolved along with societal and environmental changes. Literature supports the supposition that throughout human history, several general driving forces influence the emergence or reemergence of certain infectious diseases. The most important factors are human migration, environmental and ecological changes, changing patterns of human host susceptibility and immunity and, more recently, the use and overuse of antimicrobial agents. Table 68.1 shows some of the mechanisms identified in recent emerging infectious diseases and provides illustrative examples from the United States and abroad. In reality, many simultaneous contributing factors often are at play, and diseases may emerge or retreat within human populations without clear drivers. Common themes that result in recognizable emergence events typically couple a vulnerable host population with a pathogen to which that population lacks immunity or prior exposure.

Pediatric populations are particularly susceptible to emerging and reemerging diseases in several of these categories. The recent Zika virus epidemic has also shed light on the particular risks to the fetus in the setting of a newly emerging or reemerging infection. After immunity from acquired maternal antibody wanes, children

Table 68.1. Factors Contributing to Infectious Disease Emergence/Reemergence

Contributing Factor	*Examples*	*Illustrative Pathogens*
Societal change	Economic impoverishment Population growth or migration Globalization of food distribution Urban decay	Cholera, malaria, salmonella
Advances in health care	New medical devices Organ transplantation Drugs causing immunosuppression Use of antimicrobial agents	Aspergillosis, cytomegalovirus, methicillin-resistant *Staphylococcus aureus*
Human behavior	Worldwide travel Injection drug use Sexual activity Outdoor recreation activities	HIV/AIDS, hepatitis C virus, histoplasmosis
Environmental changes	Deforestation/reforestation Flood/drought Global warming	*Cryptococcus gattii*, dengue, *Burkholderia pseudomallei*
Public health infrastructure and control	Reduction of prevention programs Inadequate surveillance Waning immunization rates	*Mycobacterium tuberculosis* (multidrug-resistant and extensively drug-resistant), measles, mumps, pertussis
Microbial adaptation and change	Antigenic drift/shift Changes in virulence factors Development of drug resistance	H1N1, H5N1, and H7N9 influenza; chloroquine-resistant malaria; vancomycin-resistant enterococci

Derived from Morens DM, Folkers GK, Fauci AS. The challenge of emerging and re-emerging infectious diseases. *Nature*. 2004;430(6996):242–249.

develop adaptive immunity on their own and may experience up to 12 upper respiratory and/or diarrheal diseases per year. In some cases an unexplained increase in pediatric mortality from a typical clinical syndrome, such as upper respiratory or flu-like illness, may be the harbinger of an emerging pathogen. Large institutional settings, such as child care centers and schools, place children at high risk for exposure to infectious agents via close contact, and respiratory and droplet spread. Similarly, differing hygiene practices, such as handwashing, cough etiquette, sharing of fomites, and fecal/urinary incontinence, place infants and children at particular risk of exposure.

Antimicrobial agents are commonly prescribed in the primary care setting for otitis media, pharyngitis, and respiratory infection, and overuse of antibiotics in this setting has been associated with an increased risk of colonization and infection with drug-resistant organisms. In many cases, what was once a first-line therapy for a particular clinical syndrome must be reconsidered because of the emergence of altered antibiotic susceptibility patterns. Advances in medical care has resulted in growth in the number of vulnerable hosts through increased survival of preterm infants, cancer chemotherapy, organ transplantation, and the use of immunosuppressive or immunomodulatory agents. Additionally, because of parental belief systems, personal choice, and lack of access, immunization rates in certain regions remain suboptimal, placing children at risk of acquiring vaccine-preventable disease.

Special Situations

Increasingly, primary care physicians are required to carefully consider the risks of emerging or reemerging infectious diseases. Some of the unique clinical settings in which less common or emerging infectious diseases warrant consideration include expanded international travel, immigration and international adoption, immune suppression and immunomodulation, and the unvaccinated or undervaccinated child.

Expanded International Travel

With the increasing accessibility of long-distance international travel, children are more frequently being included in tourist trips or, in the case of immigrant families, visits to friends or relatives in their home country. Children are less likely to seek pretravel advice and consequently are less likely to adhere to recommended travel guidelines. A report from GeoSentinel, a large group of worldwide travel clinics, found that only 32% of children visiting friends and relatives in developing countries received recommended travel vaccines or prophylactic medications even though they were more likely to present with illness and require hospital admission after travel. Primary care physicians evaluating returning travelers must consider detailed travel history, prophylaxis or protective measures taken (if any), risk profile of the region visited, and incubation period of

the suspected pathogen. Although by far the most common travel-related illnesses are self-limited diarrheal disease, emerging infections, such as Ebola, Zika, dengue, chikungunya, and H5N1, H7N9, or H1N1 influenza, must be considered along with other infectious diseases, such as malaria and tuberculosis.

Immigration and International Adoption

Increasing rates of international adoption or recent immigration may result in evaluation by primary care physicians of children with unknown or unavailable birth, early childhood, or immunization histories (see Chapter 37 and Chapter 39). Vaccine schedules vary by country of origin, including some vaccines that are no longer given in the United States (eg, bacille Calmette-Guérin, live oral polio virus vaccine). Considerable variation exists in reliability of medical reporting in these situations, with some countries achieving or exceeding developed world standards but most providing reports of dubious quality. Many physicians who specialize in "adoption clinics" or work in settings with large immigrant populations obtain serologic evidence of prior immunization (eg, measles, mumps, varicella, polio, diphtheria, tetanus). Physicians must also be aware of infections with clinically silent latent phases (eg, viral hepatitis, latent tuberculosis, intestinal helminth infections, HIV). Several emerging or reemerging infectious diseases in the United States may be endemic in the countries of origin of adopted or recently arrived immigrant children.

Immune Suppression and Immunomodulation

Therapeutic advances in pediatric oncology, organ transplantation, rheumatology, and care of chronic congenital conditions have resulted in an increasing population of children with immunosuppression. Although typically under the care of specialists, these children may have a medical home in a primary care facility and thus can present with an opportunistic or emerging infectious disease to their primary care physician. The spectrum of risk for infectious diseases varies considerably depending on the type of immunosuppression. For example, tumor necrosis factor-α inhibitors, which are commonly used in the management of juvenile idiopathic arthritis, convey a particularly high risk of fungal and mycobacterial infection. Neutropenia from cytotoxic chemotherapy is associated with an increased risk of bloodstream bacterial infection among others. Similarly, lymphopenia related to solid organ transplantation portends a particular vulnerability to viral infections, ranging from widespread community respiratory viruses to reactivation of common agents, such as varicella-zoster virus. Emerging infectious diseases, such as new coronaviruses (Middle East respiratory syndrome coronavirus [MERS-CoV], severe acute respiratory syndrome [SARS]), human metapneumovirus, or H1N1 influenza, may have particularly severe clinical manifestations in children with immunosuppression compared with the general population.

Unvaccinated or Undervaccinated Child

Despite the ongoing efforts of public health authorities, some regions have noted a worrisome downward trend in immunization rates. Although the most widely cited study linking autism to measles, mumps, rubella (MMR) vaccination was retracted by the *Lancet* in February 2010, several recent parental surveys indicate persistent beliefs about a suspected vaccine–autism link. In 2004, the Institute of Medicine Immunization Safety Review Committee published a comprehensive report that found no convincing evidence of a causal link between the MMR vaccine or any thimerosol-containing vaccine and autism. In a survey of 1,552 parents conducted in 2009, however, 25% agreed with the statement, "Some vaccines cause autism in healthy children." Decreasing vaccination rates have resulted in increased risk for outbreaks of reemerging infectious diseases. Measles was officially declared "eliminated" (defined as the absence of endemic measles transmission for >12 months) in the United States in the year 2000. During the first 8 months of 2019, however, more than 1,200 cases of measles were reported in more than 30 states; 75% of the cases occurred in New York State, where individuals had not been vaccinated. This is the greatest number of cases reported since 1992. This compares with a median 60 cases reported annually every year from 2001 through 2011. Similar to resurgent measles outbreaks, a 2010 to 2011 pertussis epidemic in California became the largest since 1955, affecting more than 9,000 individuals and causing 10 infant deaths. Thus, it is crucial for physicians to include vaccination status and exposure history when evaluating children with an infectious syndrome. Increasingly, the differential diagnosis and diagnostic workup must include emerging and reemerging diseases, some of which may be unfamiliar to physicians from their training or clinical experience.

Select Emerging Pathogens

Major emerging and reemerging infectious diseases of the past 20 years are shown in Figure 68.1 and Table 68.2. The table is not meant to be an exhaustive list, but rather a sampling of emerging pathogens most likely to present to a primary care physician.

Viruses

Zika

Zika is a flavivirus that was initially isolated from a monkey in the Zika forest in Uganda in 1947. The geographic distribution was previously thought to be limited to Africa with mild clinical manifestations. From 2007 to 2014, however, Zika caused outbreaks in several of the Pacific Islands, after which a major epidemic emerged in Brazil in 2015 with rapid spread throughout the Americas, with outbreaks in the United States in 2016. Currently, Zika is present in more than 80 countries in Africa, Asia, and the Americas. *Aedes aegypti* as well as other *aedes* species are the primary vectors with a predilection for urban environments, similar to dengue, chikungunya, and yellow fever. Non-vector routes of transmission include blood transfusions and sexual contact.

Major features of the reemergence of Zika include both the expanded geographic distribution and discovery of its cause of severe fetal neurologic infections. Zika is neurotropic and targets neural progenitor cells in the developing brain. The resurgence of Zika in

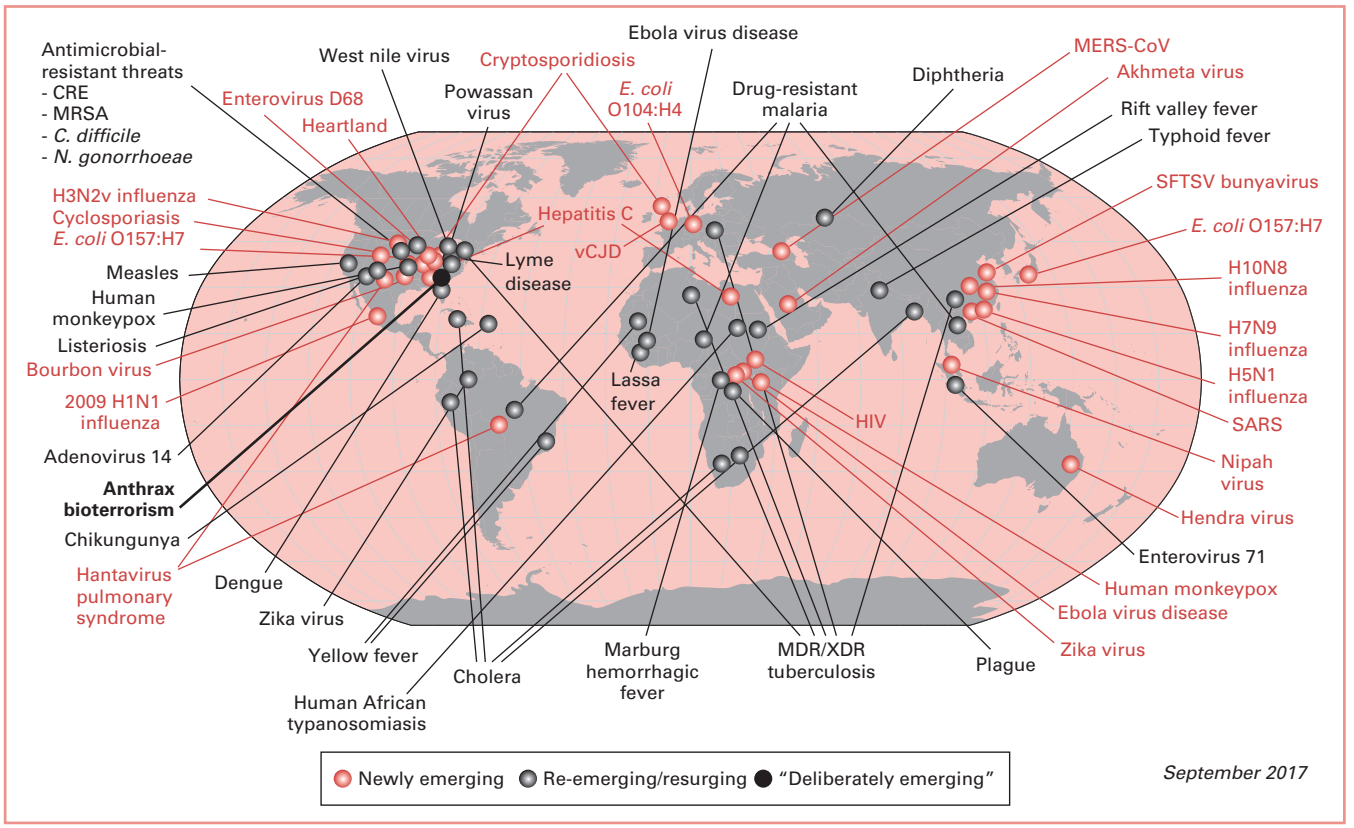

Figure 68.1. Global examples of recently emerging and reemerging infectious diseases.

Abbreviations: *C. difficile*, *Clostridium difficile*; CRE, carbapenem-resistant Enterobacteriaceae; *E. coli*, *Escherichia coli*; MDR, multi-drug resistant; MERS-CoV, Middle East respiratory syndrome coronavirus; *N. gonorrhoeae*, *Neisseria gonorrhoeae*; SARS, severe acute respiratory syndrome; SFTSV, severe fever with thrombocytopenia syndrome virus; vCJD, variant Creutzfeldt-Jakob disease; XDR, extensively drug-resistant.

Reprinted from National Institute of Allergy & Infectious Diseases. *Global Examples of Emerging and Re-Emerging Infectious Diseases*. Bethesda, MD: National Institute of Allergy & Infectious Diseases; 2017. https://www.niaid.nih.gov/news-events/three-decades-responding-infectious-disease-outbreaks

the Americas has included clinically devastating congenital central nervous system (CNS) malformations, including microcephaly, ventriculomegaly, cerebral calcifications, and ocular abnormalities. In adults, approximately 50% of infected individuals have no symptoms, with the remaining developing a rash, fever, conjunctivitis, and arthralgias. Uncommon manifestations include Guillain-Barré syndrome. The cause of the apparent shift to more prominent CNS clinical manifestations of the recent epidemics is not known. Genetic data indicate that Zika acquired a single amino acid mutation in a surface protein that causes increased neurovirulence, viral replication, and rates of microcephaly in cellular and animal models. This mutation appeared in approximately 2013 and has been stably transmitted during the epidemic. Although this genetic change may explain the new clinical manifestations, it remains possible that neurologic involvement was not previously apparent because of a lower disease incidence.

Several issues are important for clinical management of Zika, including transmission prevention, evaluation and treatment of pregnant women, and treatment of infected neonates. Prevention of vector-borne transmission includes mosquito precautions as well as avoiding or postponing travel during pregnancy. Travel-related precautions pertaining to sexual transmission extend to the post-travel time period because Zika can persist in bodily fluids (eg, RNA is detected for approximately 2 weeks in plasma, 6 weeks in urine, and up to 6 months in semen). Currently, the CDC recommends that men wait at least 3 months before engaging in unprotected sex if they are planning to conceive with their partner and may have had a Zika virus exposure. Previously, the waiting period was 6 months, but the recommendation was updated based on data indicating that the longest period from symptom onset to potential sexual transmission was 32 to 41 days. Evaluation of pregnant women for possible Zika infection includes exposure risk assessment, symptom assessment, and diagnostic testing options that are tiered based on time from exposure and stage of pregnancy. Potential diagnostic tests include nucleic acid tests in serum and urine, immunoglobulin (Ig) M serology, and a plaque reduction neutralization test. For pregnant women diagnosed with acute Zika virus infection, further diagnostic testing in the form of ultrasonography and amniocentesis can be performed to assess for fetal infection and complications. Currently, no specific treatment or vaccine is available for Zika virus.

Table 68.2. A Sampling of Recent Emerging Infectious Diseases

Pathogen	*Clinical Syndrome*	*Diagnosis*	*Management*
Zika virus	Adult: asymptomatic or viral exanthem with arthralgias Fetal: severe CNS malformations	Exposure/symptom assessment, IgM, PCR	Supportive
Ebola virus	Hemorrhagic fever	Clinical case definition Confirm on serology, PCR testing	Supportive Experimental therapies: convalescent serum, monoclonal antibodies, experimental antiviral agents, preventive vaccine
Measles virus	Measles Pneumonia Postinfectious encephalitis	Clinical Confirm with IgM	Supportive Consider antibiotics for bacterial superinfections
Mumps virus	Parotitis Orchitis Encephalopathy	Serology Culture PCR testing	Supportive NSAIDs
Dengue virus	Unspecified febrile illness Dengue fever Dengue hemorrhagic fever	Serology	Supportive Aggressive fluid management
Influenza virus (H1N1 [2009], H5N1 [2007], H7N9 [2013])	Fever, respiratory symptoms	PCR or antigen testing	Oseltamivir phosphate, zanamivir, amantadine hydrochloride, rimantadine hydrochloride
Coronavirus (ie, SARS, MERS-CoV)	Fever, respiratory symptoms	PCR testing	Supportive
Chikungunya virus	Febrile syndrome with arthralgias, rash, conjunctivitis	Clinical Confirm with serology, viral culture, or PCR testing	Supportive, NSAIDs
WNV	Asymptomatic West Nile fever West Nile encephalitis (flaccid ascending paralysis)	Serology WNV antigen or PCR testing IgM in CSF	Supportive (ribavirin and interferon-α-2b are experimental)
MRSA	Skin and soft tissue infections, bacteremia, pneumonia	Culture and susceptibility	Antibiotics
Resistant gram-negative bacteria	Pneumonia, UTI, bacteremia, sepsis	Culture and susceptibility	Antibiotics
Resistant *Streptococcus pneumoniae*	Pneumonia, meningitis, otitis media	Culture and susceptibility	Antibiotics
Ehrlichiosis/anaplasmosis	Fever, headache, myalgia, rash	PCR testing or peripheral blood smear	Doxycycline
Cryptococcus gattii	Pneumonia, meningitis	Culture or cryptococcal antigen testing	Amphotericin, 5-FC, fluconazole

Abbreviations: 5-FC, 5-fluorocytosine; CSF, cerebrospinal fluid; CNS, central nervous system; Ig, immunoglobulin; MERS-CoV, Middle East respiratory syndrome coronavirus; MRSA, methicillin-resistant *Staphylococcus aureus*; NSAIDs, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; SARS, severe acute respiratory syndrome; UTI, urinary tract infection; WNV, West Nile virus.

Ebola

First described near the Ebola river in Zaire (now the Democratic Republic of Congo [DRC]) in 1976, Ebola virus is a member of the genus *Filoviridae* of hemorrhagic fever viruses. Although until recently only seen in sporadic and remote outbreaks in sub-Saharan African villages, Ebola's reputation has far outpaced its reach because of a case fatality rate of 88% in early descriptions of the first outbreaks. Four species are known to cause disease in humans, with variable geographic footprints and virulence. *Sudan ebolavirus* has a case fatality rate of approximately 50% and has caused several moderate-sized outbreaks in the border region of Sudan, Uganda, and the DRC. *Zaire ebolavirus*, the most lethal species, has caused most of the sporadic outbreaks throughout sub-Saharan Africa, including the largest outbreak ever recorded in 2014 to 2016 that engulfed several West African countries, with approximately 28,600 cases and more than 11,000 deaths. *Bundibugyo ebolavirus* is a third species discovered in 2007 that has caused 2 well-documented outbreaks in the DRC and along the border of the DRC and Uganda. Finally, *Taï*

Forest ebolavirus has been identified in a single case in Côte d'Ivoire in West Africa. At the time of publication, an ongoing outbreak of the *Zaire ebolavirus* is occurring in the North Kivu and Ituri provinces of DRC, with at least 129 confirmed or probable cases and 89 deaths.

Although the reservoir of Ebola is unknown, scientists suspect a fruit bat or non-human primate may serve as the natural host, with uncommon "spillover events" occurring after direct human-to-animal contact. Human-to-human transmission can occur after 1 of these events via direct contact (through broken skin or mucus membranes) with infected blood or body fluids, including urine, saliva, sweat, feces, vomit, human milk, and semen. Importantly, human-to-human transmission does not occur in the absence of symptoms. No evidence exists indicating that mosquitos or other insects can transmit Ebola, and secondary foodborne transmission is not thought to occur except from direct consumption of the meat of an infected primate.

After an incubation period of approximately 8 to 10 days (range, 2–21 days), Ebola causes an array of nonspecific systemic symptoms, such as fever, nausea, vomiting, diarrhea, weakness, severe headaches, myalgias, and abdominal pain. The diagnosis should be suspected in cases with both a combination of suspected symptoms and a possible exposure to Ebola virus within the previous 21 days. Isolation of "patients under investigation" and strict contact precautions are necessary to contain outbreaks and prevent spread to health care personnel. Specialized molecular testing for viremia is available in public health laboratories and is typically positive within 3 days of the onset of symptoms.

The pathophysiology of Ebola virus disease (formerly Ebola hemorrhagic fever) involves massive fluid, electrolyte, and protein wasting as well as capillary leak and hemorrhage with resultant blood loss, dehydration, oliguria, circulatory collapse, and respiratory failure. In a well-studied case series of 27 patients evacuated from the West Africa outbreak to the United States or Europe, peak plasma viral RNA levels occurred at a median of 7 days and was cleared a median of 17.5 days after onset of symptoms. With maximal supportive care as well as experimental therapies in 85% of patients, the case fatality rate in this cohort was 18.5%, which was lower than previously reported.

Postmortem human-to-human transmission of Ebola has occurred as well, particularly related to burial rituals such as cremation, cleansing of bodies, and postmortem autopsy evaluations. The CDC has developed guidelines for safe handling of human remains focusing on the use of personal protective equipment as well as proper disposal of medical equipment and safe interment of the body. In survivors who recover from the infection, ocular complications and lingering arthralgias have been described. Persistence of virus has also been observed in immune-privileged sites, such as aqueous humor, cerebrospinal fluid (CSF), and semen; however, the transmission dynamics of convalescing patients are poorly understood.

The foundation of managing Ebola virus disease is supportive care, principally intravenous hydration and electrolyte replacement, oxygen and mechanical ventilation as necessary, renal replacement therapy, blood pressure and blood product support, and antibiotic treatment for any suspected secondary infections. After intensive ethical discussions, experimental treatments were mobilized during the 2014 to 2016 West Africa outbreak, including transfusions using convalescent serum of survivors, monoclonal antibody combinations (ie, ZMapp, ZMab, MIL77), antiviral drugs thought to have inhibitory activity against Ebola (ie, TKM-Ebola, favipiravir, brincidofovir, amiodarone), and agents purported to counteract capillary leak (ie, FX06, melanocortin). No agents have been approved by the US Food and Drug Administration for use in individuals with Ebola virus disease, and each of these cases underwent considerable ethical scrutiny and evaluation.

Prevention of Ebola virus disease has relied mainly on early diagnosis as well as strict isolation and infection control procedures. An experimental vaccine was developed and preliminarily tested in 2015 in Guinea during the large outbreak in that country. In a small trial, the vaccine appeared to be highly protective against Ebola virus disease. The National Institutes of Health is conducting an ongoing open label, pre-exposure clinical trial in adults at potential occupational risk.

Measles

Measles, which is caused by a virus from the Paramyxoviridae family, began to decline as a major threat in the United States after a safe and effective vaccine was developed in 1963. A significant resurgence occurred between 1989 and 1991, however, largely because of a pool of vulnerable, unvaccinated preschool-age children. Nearly 55,000 cases and 130 deaths occurred in the United States, prompting a renewed effort at prevention through vaccination. A second dose of vaccine for school-age children was also recommended after this outbreak. Another resurgence of new cases occurred after 2004, but with new epidemiologic features; 90% of the cases were either directly imported from travelers or immigrants, or were associated with importation from outside the United States. Large outbreaks in the United States have been reported in 2008, 2011, 2013, 2014, and 2019.

Measles is a highly contagious pathogen passed via respiratory droplets. Secondary transmission is thought to be greater than 90% among susceptible household contacts. Approximately 10 days after exposure, clinical illness is characterized by a distinctive febrile prodrome (ie, conjunctivitis, coryza, cough), followed by Koplik spots (blue-gray enanthem on buccal mucosa) and, ultimately, the classic maculopapular erythematous eruption. Diagnosis is usually ascertained based on clinical evidence alone given the distinct clinical presentation; however, for confirmatory testing, the immunoglobulin (Ig) M serology is nearly 100% sensitive if performed after the onset of rash. Respiratory droplet isolation should occur until 4 days following appearance of the rash in immunocompetent patients and until the clinical illness resolves in those who are immunocompromised. Treatment is largely supportive; however, respiratory and neurologic complications can occur in 6% and 0.1% of patients, respectively. Further control of this reemerging infectious disease will likely depend on renewed attention to domestic vaccination efforts and the roll-out of vaccination worldwide.

Mumps

Although the clinical syndrome of the mumps virus is distinct from that of measles, the 2 members of the Paramyxoviridae family share

a similar history of initial control and recent reemergence. A live, attenuated mumps vaccine was licensed in 1967 and incorporated into the Advisory Committee on Immunization Practices recommended schedule by 1977. Due to high vaccination rates, mumps had declined by more than 99% by 2005. However, there have been 2 major resurgences in the United States. In 2005 to 2006 a total of 6,584 cases were reported in a multistate outbreak in the Midwestern United States. Although numerically most of these cases occurred among college students who had been previously vaccinated, attack rates were considerably higher in unvaccinated individuals. Equally large outbreaks involving more than 6,000 cases were reported in 2016 and 2017. During the first 8 months of 2019, there were more than 2,360 reported cases in 47 states.

The clinical presentation of mumps typically involves fever, malaise, and parotitis. Complications are rare, but in some studies up to 10% of patients had aseptic meningitis, of which hearing loss is an important sequela. Up to 37% of adolescent and adult males can present with orchitis, which may result in sterility. Diagnosis is typically made based on a compatible clinical syndrome with confirmation by isolation or polymerase chain reaction (PCR)-based detection of the virus from saliva, CSF, urine, or semen. Immunoglobulin M serology is also a useful confirmatory method.

Management is generally supportive, with analgesics used for the pain of parotitis and/or orchitis. For severe cases, intravenous Ig has been used to mitigate immune-mediated postinfectious complications, and interferon-α-2b has been used to alleviate orchitis.

The previously discussed outbreaks have been the focus of considerable scrutiny as indicators of vaccine effectiveness and community vaccination rates. Based on extensive analyses, MMR vaccine is still considered to be 80% to 90% effective after 2 doses. However, a significant portion of the population remains vulnerable to occasional outbreaks. No change was made to immunization schedules or interim recommendations after these outbreaks.

Dengue

Dengue fever virus is a member of the Flaviviridae family and is known to occur in 4 serotypes. It is transmitted via a vector, usually *A aegypti,* and is present in more than 100 countries throughout the Americas, Asia, and Africa. Although historically dengue fever virus was confined to tropical and subtropical regions roughly overlapping with malarial zones, its range is expanding. In the United States, no cases of locally acquired dengue were reported between 1946 and 1980. Since 1980, sporadic cases have been reported along the United States–Mexico border, but in 2009 to 2010 a small outbreak of locally acquired dengue occurred in Key West, Florida. During the first 8 months of 2019, 408 cases were reported in the United States, with 6 additional cases in US territories. The worldwide incidence of dengue has increased at least 4-fold in the past 3 decades for unclear reasons.

Clinical manifestations occur over a wide spectrum, from asymptomatic seroconversion to severe, even fatal disease. Headache and petechial rash are common. Classically the disease is thought to occur in 3 forms: undifferentiated febrile illness, dengue fever, and dengue hemorrhagic fever. In reality, however, clinical manifestations are diverse and may include hepatitis, myocarditis, pericarditis, and encephalopathy. Leukopenia and thrombocytopenia are common laboratory findings, and in severe cases, a coagulopathy and bleeding manifestations seem to be the most dangerous sequelae. Diagnosis can be made with a compatible clinical history and confirmed on serologic testing. No direct-acting antivirals exist, nor is a vaccine available. Care is generally supportive.

Influenza Viruses

In 2009, a novel strain of influenza A known as H1N1 caused the first global influenza pandemic since 1968, with an estimated 59 million illnesses and 12,000 deaths in the United States alone. Although early in the year it seemed as though "bird flu" or H5N1 influenza would be the greatest concern to public health, it was a different strain of swine origin that resulted in a global pandemic. In April 2013, a different strain of bird flu known as H7N9 emerged in China with a disturbing 28% case fatality rate. Like the related H5N1 strain, however, human-to-human transmission was not observed, and outbreaks have been limited to clusters of individuals with very high levels of exposure to poultry.

Influenza viruses have a segmented genome and thus are able to adapt and evolve quite rapidly to evade slower adaptive immune responses. Through antigenic drift, small changes occur in cell surface genes through time, resulting in subtle structural changes to the cell surface proteins neuraminidase and hemagglutinin and decreased recognition by the immune system. In antigenic shift, genome segments from diverse strains recombine in a single new virus particle, resulting in abrupt and substantial changes in antigenic variation. Typically, shifts are more likely to cause pandemics because of the increased number of nonimmune hosts in the population.

Although the clinical manifestations of H1N1 influenza seemed to be similar to those of prior influenza outbreaks, this strain resulted in more severe cases and higher mortality in previously healthy young people than in typical influenza epidemics. Testing for H1N1 most commonly involves antigen-based PCR methods with variable sensitivities and specificities. Management of severe cases consists either of oral oseltamivir phosphate or inhaled zanamivir. Although oseltamivir phosphate resistance outside the United States has been reported, it remains the drug of choice.

The more recently recognized H7N9 strain seems to be more virulent than H1N1, with a high proportion of patients presenting with severe pulmonary manifestations. In the preliminary reports of the first 111 patients in China, 77% were admitted to an intensive care unit and 28% died. Because of the ability of influenza virus to change rapidly with genetic drift and shift, health officials are on alert for any increase in H7N9 activity in the fall influenza season. The 2018 to 2019 influenza season was moderately severe, and the 21-week season was longer than seasons from the prior 10 years. The 2 major strains were H1N1 and H3N2.

Chikungunya

A vector-borne disease transmitted primary by *Aedes* species mosquitoes, chikungunya was first described in Tanzania in 1953. It

often occurs in epidemic outbreaks rather than steady endemic patterns and is most commonly seen in tropical Africa and Asia. More recently, outbreak ranges have expanded slightly, occurring in Italy and Madagascar. Chikungunya virus disease became a nationally notifiable condition in 2015. A total of 156 chikungunya virus disease cases with illness onset in 2017 have been reported from 28 US states. All reported cases occurred in travelers returning from affected areas. No locally transmitted cases have been reported in the United States. The clinical hallmark of chikungunya fever is the presence of intense arthralgias and occasionally frank arthritis after a febrile illness with rash and conjunctivitis. Whereas the clinical illness of malaise and fever may last days to weeks, the joint symptoms may last months to years. Other than the possibility of persistent and nagging arthralgias, severity is typically mild, and fatality is rare. Management of chikungunya is generally supportive, because no specific antiviral agents are available.

Coronaviruses: Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome

From 2002 to 2004, an epidemic of severe pneumonia resulting from a previously unrecognized coronavirus (ie, SARS-CoV) caused considerable international concern because of its highly infectious nature and high mortality rate. Epidemiologic studies resulted in identification of palm civets as the main reservoir of transmission to humans from contact in the marketplace. Further studies suggested that horseshoe bats were the likely natural reservoir. The epidemic, which originated in China, eventually spread to 29 countries with an overall mortality rate of 9.6%, which included numerous health workers. Clinical features included a mean incubation period of 4.6 days, with a presentation of severe pneumonia with a high rate of respiratory failure. Additional clinical manifestations included watery diarrhea and hepatitis. Common laboratory features included lymphopenia, neutropenia, and disseminated intravascular coagulation. The cornerstone of management was supportive care. Although many individuals received ribavirin, no proven role for it or any antiviral agent existed during the outbreak. Despite the impressive nature of this epidemic, it subsided rapidly and no evidence exists of ongoing SARS-CoV transmission. This epidemic highlighted an agent with high transmissibility, morbidity, and mortality but with only a transient global impact.

In 2012, a second emerging coronavirus was identified as the cause of a severe acute respiratory infection in a patient in Saudi Arabia. From 2012 to 2013, 130 cases were reported, all of which involved direct or indirect travel or residence in 4 countries: Saudi Arabia, Qatar, Jordan, and the United Arab Emirates. The reservoir has not been conclusively established yet, although a zoonotic origin has been suggested resulting from the identification of related coronaviruses in bats and camels. As of 2017, approximately 2,000 cases have been confirmed in countries in the Arabian peninsula. The clinical features include an incubation period of 5.2 days with symptoms that range from none or mild to severe disease, including death in 45% of reported cases. A large proportion of patients (96%) have underlying comorbidities, and 80% required ventilatory support.

Bacteria: Drug-Resistant

Community-Acquired Methicillin-Resistant Staphylococcus Aureus

Methicillin-resistant *S aureus* (MRSA) strains were recognized shortly after the introduction of methicillin in the 1960s and have been a substantive problem in health care settings for several decades. Health care-associated MRSA (HA-MRSA) has well-established risk factors, including exposure in the health care setting (eg, hospital, nursing facility) and the presence of comorbid medical conditions (eg, malignancy, chronic liver or lung disease, indwelling catheters). In the 1990s, a new strain of community-acquired MRSA (CA-MRSA) appeared that was not associated with these traditional risk factors, because often it was found in otherwise healthy individuals with no health care–related exposure. Furthermore, CA-MRSA carries the *mecA* resistance gene on a type IV or V cassette chromosomes in contrast to HA-MRSA, which carries type I through III cassette chromosomes. Community-acquired MRSA is also more likely to contain the Panton-Valentine leukocidin genes, which may encode virulence factors that influence clinical symptoms. These genotypic differences have facilitated epidemiologic studies that suggest that CA-MRSA is a distinct MRSA strain that has increased in frequency throughout the United States and is a bona fide emerging pathogen. In addition to genotypic differences, CA-MRSA is less likely than HA-MRSA to have a multidrug–resistant susceptibility pattern. Treatment of CA-MRSA follows similar principles to HA-MRSA with the exception that more antibiotic choices are generally available. For an uncomplicated cutaneous abscess, incision and drainage without antibiotics is often sufficient. For deeper or more severe infections, empiric treatment with trimethoprim-sulfamethoxazole, clindamycin, a tetracycline (doxycycline or minocycline), or linezolid are empiric options while awaiting antibiotic susceptibilities. Although linezolid is an effective drug, it is far more expensive than the other choices. Tetracyclines should not be used in children younger than 8 years. For impetigo and other minor infections, topical mupirocin can be used.

Resistant Gram-Negative Bacteria and Streptococcus Pneumoniae

Similar to CA-MRSA, other resistant bacteria have established significant niches. For example, *S pneumoniae* was historically uniformly sensitive to penicillin. Currently, penicillin- and ceftriaxone-resistant strains of *S pneumoniae* are now common and circulating in the community. Similarly, several gram-negative bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae,* are highly resistant because of a variety of plasmid and chromosomally encoded mechanisms, such as β-lactamases, cephalosporinases, carbapenemases, porins, and efflux pumps. These strains are most common in the nosocomial setting, although community circulation of these strains has also occurred. Although the emergence of these strains is not as extensive or as clearly delineated as CA-MRSA, each of these strains has similarly "emerged" to a prevalence level in the population that substantially affects human health.

Ehrlichiosis and Anaplasmosis

Ehrlichia chaffeensis, the etiologic agent of human monocytic ehrlichiosis (HME), and *Anaplasma phagocytophilum*, the etiologic agent of human granulocytic anaplasmosis (HGA [formerly human granulocytic ehrlichiosis]), are examples of infections that were identified after the development of new diagnostic tests. Both infections were initially recognized as infections of the veterinary world until the application of molecular methods to humans with undiagnosed febrile illnesses. These infections likely have caused human disease for a long time, although the incidence may have increased with the recent resurgence of populations of some animal reservoirs, such as the white-tailed deer. In the early 1990s, *E chaffeensis* and *A phagocytophilum* were identified as human pathogens that are transmitted by ticks. *Ehrlichia chaffeensis* is transmitted by several ticks (ie, *Amblyomma americanum*, *Dermacentor variabilis*, *Ixodes pacificus*) and is found in the Southeastern and South Central United States as well as California. *Anaplasma phagocytophilum* is transmitted by *Ixodes scapularis* and is found in the northern United States. Both agents cause a febrile illness with headache, myalgia, and malaise that is often accompanied by thrombocytopenia, leukopenia, and transaminitis. Rash, which occurs in 90% of subjects with Rocky Mountain spotted fever (caused by *Rickettsia rickettsii*), is less often found with HME (31%) and rarely with HGA. Diagnosis of these infections can be made by PCR testing and less commonly with direct microscopy because the latter methods are insensitive (<10% for HME and 25%–75% for HGA). Because of the potential severity of the illness, however, if clinical suspicion is high empiric treatment should be initiated while awaiting the diagnostic workup. Doxycycline is the drug of choice for management of HGA and HME. Because of a lack of reliable alternative drugs, doxycycline is recommended for children younger than 8 years as well.

Fungi: *Cryptococcus Gattii*

Cryptococcus gattii (formerly *Cryptococcus neoformans* var *gattii*) and *C neoformans* are yeast that cause pneumonia and CNS infections in immunocompetent and immunocompromised hosts. Although *C neoformans* is present in most regions of the world, *C gattii* has a restricted geographic distribution and previously had been identified in tropical and subtropical countries such as Australia, New Zealand, and Papua New Guinea. In the early 2000s, *C gattii* was identified as a cause of meningoencephalitis for the first time on Vancouver Island in British Columbia. From 1999 to 2007, 218 cases were reported, with a case fatality rate of 8.7%. Subsequent studies identified its presence in the Pacific Northwest, including the states of Washington and Oregon. Similar to many emerging pathogens, the increased number of cases may be the result of improved diagnostics and surveillance as opposed to the actual emergence of a new infection to a region. Some molecular evidence suggests that the strain on Vancouver Island is novel, however. Clonal analysis suggests that it arose from an unusual type of sexual mating that generated a hypervirulent strain. This mechanism of emergence suggests that a species endemic to an original location (eg, tropics) can emerge in a new geographic region (eg, Vancouver Island) in a clonal manner. The clinical presentation of *C gattii* is similar to *C neoformans*, although *C gattii* may be associated with an increased frequency of cryptococcoma in the lungs and CNS. Treatment principles are the same for both species and include initial management with amphotericin B and 5-fluorocytosine for meningitis followed by consolidation therapy with fluconazole. For uncomplicated pulmonary disease, fluconazole is the cornerstone of treatment. *Cryptococcus* species, including *gattii*, infect children as well, and treatment principles are similar to those for adults.

Summary

Contrary to myopic claims that public health would conquer infectious diseases in the 20th century, new pathogens have continued to emerge and old ones have reemerged time and time again, making for a challenging future of disease identification and control. Transcontinental air travel has made even the most remote areas of the world reachable within 24 hours, bringing the distant populations much closer and exponentially increasing the potential for disease transmission and outbreak propagation. The tools used by public health include surveillance and response; however, most of the major epidemics identified in the past 20 years began with astute clinical observation at the primary care level. Thus, it is essential for primary care physicians and others caring for children to remain vigilant to the constant and unpredictable nature of emerging infectious diseases. With astute primary care physicians, attentive scrutiny of new outbreaks, and collaboration with regional and national public health laboratories and officials, it is hoped that the medical field will keep pace with emerging and reemerging pathogens.

CASE RESOLUTION

The patient was hospitalized and underwent an extensive diagnostic workup for infectious causes of fever and rash. A lumbar puncture revealed mild lymphocytic pleocytosis. The patient received 2 days of empiric antibiotic therapy, which was discontinued when cultures were negative for 48 hours. The pediatrician notified the local health department, which facilitated laboratory testing performed by the state public health laboratory, and the CDC.

Serologic testing at the state health department was positive for IgM antibodies against dengue virus. This was confirmed on samples sent to the CDC; additionally, based on reverse-transcriptase PCR testing, CSF sent to the CDC was found to be positive for dengue virus serotype 1. The patient recovered uneventfully in the following 2 weeks, but a public health investigation was launched that eventually resulted in the identification of 27 total cases of dengue fever acquired in Key West. Subsequently, an adult serosurvey was conducted indicating recent exposure to dengue in 5.4% of the adults studied.

This outbreak, which occurred in 2009 to 2010, represented the first reported cases of dengue fever acquired in Florida since 1934. Although dengue is the most common virus transmitted by mosquitoes in the world, no cases had been acquired in the continental United States between 1946 and 1980 and, subsequently, only sporadic cases were known along the United States (specifically, Texas)–Mexico border. Reported dengue cases have increased 4-fold in Latin America since 1980, and incidence has risen steadily among returning travelers from the United States. Dengue represents a truly reemerging infectious disease, and primary care physicians should be aware of its rising incidence.

Internet Resources

American Academy of Pediatrics. *Red Book: 2018-2021 Report of the Committee on Infectious Diseases*
https://redbook.solutions.aap.org

Centers for Disease Control and Prevention
www.cdc.gov

Dengue. Centers for Disease Control and Prevention
www.cdc.gov/dengue

Ebola. Centers for Disease Control and Prevention
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CHAPTER 69

Febrile Seizures

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CASE STUDY

A 12-month-old girl is brought to the emergency department by paramedics because she is having a seizure. She is unresponsive and hypertonic, with arched trunk and extended arms and legs that are jerking rhythmically. Her eyes are open, but her gaze is directed upward. She has bubbles of saliva around her lips as well as circumoral cyanosis. Her vital signs are a respiratory rate of 60 breaths/minute, heart rate of 125 beats/minute, blood pressure of 130/78 mm Hg, and temperature of 41.0°C (105.8°F). An assessment of her respiratory status shows that she is moving air in all lung fields, and no evidence exists of upper airway obstruction.

The paramedics inform you that the girl has been convulsing with varying intensity of tone and movements but has remained unresponsive for approximately 6 minutes. Glucometer testing reveals a normal serum glucose level. Blood samples for other tests are sent to the laboratory, and urine is collected. An intravenous (IV) line is started, and the girl is given lorazepam by IV push. Within 2 minutes the movements cease, and her respirations become slow and even. No signs of trauma are evident on physical examination. Her only abnormality other than her unresponsive mental status is an inflamed and bulging right tympanic membrane.

The girl's parents tell you that she has had a mildly stuffy nose for 2 days but has been afebrile and has seemed to be her usual self. While she was playing she became irritable, and her parents put her in her crib for her nap. Thirty minutes later they heard grunting noises, found her in the midst of a seizure, and called the paramedics. This is the girl's first seizure. Her father recalls that his mother once told him that he had several "fever seizures" as an infant.

Questions

1. What are the characteristics of simple febrile seizures versus complex febrile seizures?
2. What is the appropriate evaluation of the child with febrile seizure, whether it is the first or a recurrence?
3. What is the recurrence risk for febrile seizure and the risk of developing unprovoked seizures after a febrile seizure?
4. What are the management options for the child with febrile seizure?

Febrile seizures are easily recognized, dramatic, generalized convulsions. A *febrile seizure* is defined by the presence of a fever or an acute inflammatory illness (often sudden) from a source outside the nervous system; patient age of approximately 5 years or younger; absence of chronic brain pathology, including developmental delay; absence of metabolic or structural abnormalities of the brain; and absence of previous nonfebrile seizures. Frequently, familial predisposition to similar seizures or a history of similar events in other family members is present. Despite the relatively uniform presentation of the seizure, other factors, such as genetic abnormalities in channels, neurotransmitter receptors, or hippocampal damage may influence prognosis, and individual clinical variables and social factors may influence management.

Epidemiology

Febrile seizures occur in children between 6 months and approximately 5 years of age, but they are more common in children younger than 3 years. Some studies indicate that as many as 5% of all children in the United States experience at least 1 febrile seizure, and the prevalence is higher in the Asian population (eg, 6%–9% in Japan). The recurrence rate is 30% to 50% in children younger than 1 year, drops to 25% between 1 and 3 years of age, and falls to 12% after age 3 years. Seizures are associated with a higher maximum temperature and may occur with the rise in temperature and often so suddenly that the febrile illness is not recognized by the family prior to the seizure. Frequently, the febrile illness eventually is diagnosed as an upper respiratory tract or influenza infection or follows immunization. Human herpesvirus 6 infections may be associated with one-third of first-time febrile seizures and a somewhat higher rate of complex febrile seizures. Febrile seizures often occur in children with a first-degree relative who experienced the problem at the same age.

Clinical Presentation

A *simple febrile seizure* is characterized by a single episode of generalized, symmetric, tonic posturing and clonic movements of a few minutes' duration that occurs suddenly in the child whose developmental progress is generally normal. Fever or an acute inflammatory illness is present, although it may not have been recognized before the seizure, and its source is outside the nervous system. A short time after the seizure (typically after 1–2 hours of postictal sleepiness), the child returns to a normal neurologic state (Box 69.1).

Box 69.1. Diagnosis of Febrile Seizure in the Pediatric Patient

- Sudden unresponsiveness, tonic posturing, and generalized rhythmic jerking
- Fever or acute inflammatory illness source outside nervous system
- Age 6 months to approximately 5 years
- Normal neurodevelopmental history

The recently described *generalized epilepsy with febrile seizures plus* (GEFS+) is characterized by the association of generalized febrile seizures after age 6 years and afebrile generalized convulsions, a positive family history of epilepsy with variable phenotypes, and a benign prognosis in most cases. The same families may have simple febrile seizures, febrile seizures after age 6 years, febrile seizures and absences, atonic or myoclonic seizures, and myoclonic-astatic epilepsy or Dravet syndrome.

Pathophysiology

The susceptibility of young children to febrile seizures may be related to an increased incidence of sudden high fevers in this age group, a developmental genetic factor that may lower the seizure threshold, or both. Animal models indicate that the immature brain has a lower seizure threshold than the adult brain, and seizures in the immature brain are more likely to occur by a mechanism different from that in the adult. Febrile seizure has a mild association with prenatal nicotine exposure, iron insufficiency, and atopic conditions. A sudden increase in temperature to a sufficiently high level can provoke seizure regardless of age. Cultured neurons subjected to hyperthermia show epileptiform activity. Seizures occur more frequently with fever in many seizure-prone patients who have seizures of different etiologies, including genetic epilepsies. It may be that circulating pyrogens or interleukins interact with a brain cellular circuitry mechanism or susceptible ion channels, causing hypersynchronous depolarization and seizure. The commonly noted multigenerational familial history is suggestive of a dominantly expressed genetic transmission with reduced penetrance or a polygenic model. Different families have different loci linkages.

The precise definitions of the genetic markers and mechanisms of generalized seizures in all cases are not yet fully understood. Recent work suggests possible mechanisms. Mutations in γ-aminobutyric acid $(GABA)_A$ receptor genes have been found to be associated with febrile seizures and GEFS+ pedigrees. The $GABA_A$ receptors transmit inhibitory signals and are composed of combinations of 5 subunits. The γ2 subunit is critical for receptor trafficking, clustering, and synaptic maintenance, and mutations in this subunit have been associated with febrile seizure families. It has also been found that the trafficking of mutant receptors with γ2 subunit mutations was more highly temperature dependent than mutations of other subunits and impaired membrane insertion or accelerated receptor endocytosis when brief increases of 37°C to 40°C (98.6°F to 104°F) occurred. In families with these mutations, febrile seizures may be caused by a fever-induced change in the status of a dynamic membrane receptor system, producing reduced numbers of available $GABA_A$ receptors.

In other families with GEFS+, it has been found that mutations in the *SCN1A* (sodium voltage-gated channel alpha subunit 1) gene have occurred. Mutations in this same gene may occur in sequences that encode for the critical "pore" region of the subunit protein that participates in ion selectivity and results in a more severe phenotype with early prolonged resistant seizures and later, intellectual and developmental disability and Dravet syndrome. A less severe GEFS+ phenotype is associated with a less functionally critical position of the missense mutation in the *SCN1A* gene. A rat model of hyperthermic seizures has a comparable mutation and may provide additional clues related to pathophysiology.

Differential Diagnosis

When a young child presents with a fever and a seizure, the possibility that the seizure is symptomatic of meningitis, encephalitis, or brain abscess must be considered, although other clinical signs are nearly always present. Signs of meningeal irritation may not be reliable in infants younger than 12 months, however, and these and other signs of the illness may be obscured in the postictal period. If a history of lethargy or persistent vomiting exists; the seizure is focal in onset or prolonged or multiple seizures occur; or the postictal depression is prolonged, an examination of the cerebrospinal fluid (CSF) should be done. In addition, if the patient is deficient in *Haemophilus influenzae* type b or *Streptococcus pneumoniae* immunizations or the patient has been pretreated with antibiotics, which could mask meningeal signs or symptoms, a CSF examination should be considered. It is rare that a febrile seizure would cause CSF pleocytosis (>10–20 white blood cells/mm^3). The fever also could be provocative or coincidental to a seizure of different etiology, such as trauma, toxic ingestion, metabolic derangement, degenerative or neurocutaneous disorder, or stroke.

A useful concept for the physician caring for a child with a febrile seizure has been the differentiation of simple febrile seizure from complex febrile seizure (Table 69.1). A question with prognostic implications is whether a child in the appropriate age range has had a true febrile seizure or a seizure with fever, which may be an early fever-provoked episode of a nonfebrile seizure disorder. The factors that define a complex febrile seizure also predict an increased likelihood of later unprovoked nonfebrile seizures. A complex febrile seizure may last 15 minutes or longer. Most febrile seizures are shorter than 90 seconds, although a significant number present in status epilepticus. Recurrent febrile seizures are considered complex if more than 1 febrile seizure occurs during the same infectious illness or during the first 24-hour period following the initial seizure. Febrile seizures are also complex if there is a history of a focal or partial onset or the presence of postictal focal neurologic signs. An abnormal neurodevelopmental history prior to the febrile seizure or abnormal neurologic examination or brain imaging study before or after the seizure also is indicative of an increased likelihood of later unprovoked seizures.

Table 69.1. Simple Versus Complex Febrile Seizures

Feature	*Simple*	*Complex*
Onset of clonic movements	Generalized	Focal
Length	<15 minutes (usually <90 seconds)	≥15 minutes
Number of seizures per 24-hour febrile illness	1	Recurrent
Neurodevelopmental history	Normal	Abnormal
Parent or sibling history of febrile seizure	Often positive	Often negative

Evaluation

History

After the seizure has been controlled and the child has been stabilized, a more detailed history relating to the circumstances of the seizure should be obtained, including the child's state leading up to the seizure; prenatal, birth, and developmental histories; and family seizure history (Box 69.2).

Physical Examination

The child should be examined thoroughly after stabilization, noting the possibility that the fever may be coincidental and signs from an unrelated cause inciting the seizure could be present. The physician should look for bruising, fracture, retinal hemorrhage, and other signs of trauma. The presence of dysmorphic features, enlarged organs, or bony changes should be noted. The skin should be examined for abnormal, pigmented, or textured spots. Lateralized signs of tone or strength should be assessed. An appropriate examination to determine the etiology of the fever should also be performed (see Chapter 67). Meningismus, bulging fontanelle, and prolonged postictal drowsiness should prompt consideration of meningitis or encephalitis.

Laboratory Tests

If the seizure is prolonged, focal, or multiple; if a history exists of lethargy, stupor, or persistent vomiting before the seizure; or if the patient remains ill-appearing after the postictal period, cultures should be obtained and metabolic and toxicologic blood and urine studies sent. A lumbar puncture for CSF examination for meningitis or encephalitis should be done unless signs exist of increased intracranial pressure or a lateralized neurologic examination, in which case antibiotics should be given and an imaging study obtained prior to the lumbar puncture.

If the seizure is a simple febrile seizure, without history or signs of dehydration, blood tests are of low yield. Likewise, electroencephalography has limited usefulness. The record is often abnormal in a nonspecific way and not helpful in predicting future simple febrile seizures or epilepsy. If the patient does not fully recover after the postictal period, electroencephalography may be useful to help define the nature of the encephalopathy.

Genetic testing for *SCN1A* mutations may be considered for the child with GEFS+.

Imaging Studies

Computed tomography and magnetic resonance imaging have a low yield of abnormal results in children with simple febrile seizures. However, for the child with a persistently abnormal neurologic examination or signs of increased intracranial pressure, or with an abnormal neurodevelopmental history or a focal or partial onset to seizure, an imaging study should be performed to detect a structural lesion that may be acute and the source of the present seizure and that may serve as a nidus for future seizures.

Management

If the child is still convulsing on presentation and has been for at least 5 minutes, the condition should be managed as for status epilepticus (see Chapter 131). The airway must be secured, blood drawn and sent to the laboratory for testing, an intravenous line started, and lorazepam administered in the appropriate dose to stop the seizure.

If the child is not in status epilepticus, treatment decisions are made based on a more long-term outlook (Box 69.3). Whether or not to recommend anticonvulsant prophylaxis for the child who has experienced febrile seizures is controversial. Factors that must be considered include the benign, age-limited nature of the condition; the morbidity of the anticonvulsant treatment; the chance of recurrence of febrile or nonfebrile seizures; the risk

Box 69.2. What to Ask

Febrile Seizure in the Pediatric Patient

- What were the child's symptoms for the few days before the seizure?
- Where was the child, and what was the child doing immediately before the seizure?
- Were there any pregnancy-related or perinatal complications?
- Has the child's development been normal or similar to that of siblings?
- Have any other family members had seizures of any kind, including during infancy?

Box 69.3. Treatment Options for the Pediatric Patient With Febrile Seizure

- Cooling measures during febrile illness (ie, antipyretic agents or bathing in tepid water)
- Family reassurance and education
- Diazepam, 0.3 mg/kg orally or 5–10 mg rectal gel (eg, Diastat) every 8 hours (during febrile illness only)
- Phenobarbital, 3–5 mg/kg orally daily, for prophylaxis
- Valproic acid (divalproex sodium), 30 mg/kg orally divided twice daily, for prophylaxis

of overmedication during an acute recurrence; and the family's reaction and social disruption caused by the seizures. Given the combination of these factors, particularly the weight of the first 2, most physicians do not recommend antiepileptic drug prophylaxis for febrile seizures.

Daily dosing of phenobarbital or valproic acid is an effective form of anticonvulsant prophylaxis. The most commonly used regimen is daily phenobarbital; however, the potential side effects of this agent include attention-deficit/hyperactivity disorder and depressed cognition and learning. Valproic acid can produce thrombocytopenia and may have the potential of provoking acute liver dysfunction in a patient younger than 2 years who is taking other medications. Fever control measures should be instituted to make the patient more comfortable, but these have not been found to be effective as prevention for seizures. Intermittent anticonvulsant therapy with diazepam or clobazam has the advantage of reducing (but not always eliminating) the side effects of hyperactivity, lethargy, ataxia, and sedation; however, this regimen is reliant on recognizing the fever before the seizure and mandates greater vigilance for compliance during each fever. Additionally, the evidence of this approach for reducing recurrence risk has been shown to be inconsistent at different ages. Because prolonged febrile seizures tend to recur as repeated prolonged seizures, such patients may benefit from the availability of rectal diazepam or intranasal midazolam to administer at home as an abortive drug to stop the seizure earlier in its course while paramedics are being called.

Recommendations for prophylactic anticonvulsant treatment are often individualized. Anticonvulsants usually are not recommended unless the child has presented in status epilepticus, has experienced marked respiratory compromise (perhaps needing ventilatory support) during the seizure, or has had complex febrile seizures. No definitive evidence exists that anticonvulsant prophylaxis for simple febrile seizures prevents the development of unprovoked seizures. The child who has had frequently recurring seizures that are extremely disruptive for the family and deleterious to parent-child interactions despite educational efforts by medical caregivers may also be a candidate for prophylactic anticonvulsant treatment, including the use of oral or rectal diazepam (eg, Diastat) every 8 hours during the febrile illness.

Prognosis

Febrile seizures are a common age-limited problem. The prognosis for children with simple febrile seizures is generally good and not associated with permanent neurologic deficits; the incidence of seizure episodes later in life is 3 to 6 times higher than in the general population at the same age but is still low (2% to 3%). Patients with complex febrile seizures have a higher likelihood of developing a nonfebrile seizure disorder (ie, epilepsy) compared to patients with simple febrile seizures; however, this risk is only 6% if 2 of the first 3 factors listed in Table 69.1 are present or 17% if the patients have neurodevelopmental abnormality. Overall, one-third of children with febrile seizures experience a febrile seizure recurrence. The risk of febrile seizure recurrence is most dependent on age: 50% of infants younger than 1 year at the time of their first seizure will have a recurrence, but only 20% of children older than 3 years will have a recurrence. Other factors that have a lesser influence on the recurrence risk include family history of febrile seizures but not epilepsy, temperature at the initial seizure, time since the previous seizure, and history of previous recurrences.

Animal models suggest that in the immature brain, seizures—even status epilepticus episodes—are less often associated with neuronal death; however, seizures, particularly hyperthermic seizures, can modify brain development by altering cortical motor maps and the expression of ion channels and inhibitory receptor subunits that regulate neuronal excitability. Additionally, epileptogenic mechanisms may be more robust in the immature brain than in the adult brain. However, children with febrile convulsions have shown no difference in later academic progress or behavior compared with control children.

Evidence suggests that complex febrile seizures are associated with temporal lobe epilepsy in some cases. A history of prolonged complex febrile seizures is reported in 30% of patients with mesial temporal sclerosis (MTS) who underwent surgery for intractable temporal lobe epilepsy; this is in contrast to only 6% of patients with complex febrile seizures who did not have MTS. It is possible that MTS is the consequence of prolonged febrile seizure when the hippocampus is developmentally vulnerable. Mesial temporal sclerosis is frequently unilateral and focal complex febrile seizures originate in the temporal lobe in some children; additional evidence is suggestive of causality. An alternative explanation is that some preexisting hippocampal malformation, genetic predisposition, or subsequent damage may be present in the patient with hippocampal sclerosis and prolonged febrile seizures and that the complex febrile seizure is a collateral phenomenon. Ten percent of children who present with febrile status epilepticus have evidence of hippocampal malrotation.

A small percentage of infants with febrile seizures may develop Dravet syndrome, a phenotype influencing neurocognition as well as later medication-resistant epilepsy, if they carry a particular channel subunit gene mutation. Additionally, a quite rare consequence of prolonged focal febrile seizures is hemiconvulsion-hemiplegia-epilepsy syndrome, which is characterized by unilateral swelling and later cerebral hemiatrophy of the epileptic hemisphere.

CASE RESOLUTION

The girl had a somewhat prolonged simple febrile seizure, a diagnosis that was supported by a positive family history for febrile seizures. Her family is educated about treatment options. They are comfortable with a decision to use only rectal diazepam for a subsequent febrile seizure lasting longer than 5 minutes.

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CHAPTER 70

Respiratory Distress

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CASE STUDY

A 6-month-old boy has been coughing and breathing fast for the past day. This morning he refused feeding and has been irritable. On examination, the infant is fussy. He has an oxygen saturation of 92%, a respiratory rate of 60 breaths per minute, a pulse of 140 beats per minute, and a normal blood pressure and temperature. Additionally, he has nasal flaring, intercostal and supraclavicular retractions, and occasional grunting.

Questions

1. What are the causes of respiratory distress in infants and children?
2. What are the signs and symptoms of respiratory distress in infants and children?
3. What are the signs and symptoms of impending respiratory failure in infants and children?
4. What are the critical interventions for infants and children in respiratory distress?

Respiratory distress and respiratory failure may cause significant morbidity and mortality in infants and children. The signs and symptoms of respiratory compromise may be subtle, particularly in small infants and early on. Decompensation may occur rapidly if ventilation or oxygenation is inadequate but may be prevented by prompt recognition and management. *Respiratory distress* is defined as increased work of breathing, and it usually precedes respiratory failure. *Respiratory failure* occurs when ventilation or oxygenation is insufficient to meet the metabolic demands of the tissues (ie, oxygenation of the blood is inadequate or carbon dioxide is not eliminated). Respiratory failure may be caused by diseases of the airway, inadequate gas exchange in the lungs, or poor respiratory effort (Box 70.1). Respiratory failure may result in cardiopulmonary arrest if not corrected promptly.

Epidemiology

Primary care physicians frequently care for children in respiratory distress in offices and emergency departments. Respiratory distress remains the most common reason for hospital admission. Such admissions usually involve young infants with acute infections, such as bronchiolitis or croup. Reactive airways disease (eg, asthma) is a common reason for respiratory distress-related admission in older children.

Clinical Presentation

Increases in respiratory rate and work of breathing are the most common signs of respiratory disease. Tachycardia is often present; the presence of bradycardia, however, may be an ominous sign of impending cardiopulmonary failure and arrest. Effortless tachypnea (ie, Kussmaul breathing) may be a sign of respiratory compensation for metabolic acidosis rather than an indication of pulmonary pathology. Similarly, hypoxia that does not improve with supplemental oxygen may be suggestive of a primary cardiac lesion. Signs of poor oxygenation include alterations in mental status, head bobbing, and change in skin color. Pallor, mottling, and cyanosis are often late signs of respiratory failure and shock. The child with severe hypoxemia may initially appear dusky or pale. If the child is anemic, cyanosis may not be evident even in the presence of low oxygen saturation (Box 70.2).

Pathophysiology

The adequacy of respiration depends on the ability to move an adequate volume of gas in and out of the airways as well as effective gas exchange of carbon dioxide and oxygen. Infants and children generally breathe with minimal effort. In very young children, the diaphragm and abdominal musculature are primarily used for ventilation, and the tidal volume is approximately 6 to 8 mL/kg. If the tidal volume is decreased because of obstruction, children compensate by increasing the respiratory rate, thus attempting to maintain adequate minute ventilation (minute ventilation = rate × tidal volume). If the minute ventilation remains insufficient for adequate gas exchange or the child can no longer sustain the increased work of breathing, respiratory failure ensues. Respiratory failure may then result in acidosis, myocardial dysfunction, and shock and may progress to complete cardiopulmonary arrest.

Infants and children are more prone than adults to respiratory distress because of the differences between their respiratory systems (Box 70.3).

Differential Diagnosis

The differential diagnosis of children with respiratory distress can include abnormalities with the pulmonary, cardiovascular,

Box 70.1. Common Causes of Respiratory Distress in Infants and Children

Upper Airway
- Aspirated foreign body
- Croup
- Epiglottitis
- Anaphylaxis
- Airway anomalies or immaturity

Lower Airway
- Reactive airways disease (eg, asthma)
- Bronchiolitis
- Pneumonia
- Pulmonary edema

Metabolic
- Acidosis
- Anemia

Cardiac
- Congenital heart disease
- Congestive heart failure
- Dysrhythmia
- Pericarditis or tamponade

Neurologic
- Central
- Peripheral
- Neuromuscular

Traumatic
- Chest wall injury
- Pneumothorax, hemothorax, or pulmonary contusion
- Submersion injury
- Smoke inhalation
- Toxin exposure or ingestion

Box 70.2. Respiratory Distress

- Increased respiratory rate
- Poor feeding
- Inability to speak in sentences
- Changes in tidal volume or minute ventilation
- Nasal flaring
- Presence of retractions: intercostal, substernal, diaphragmatic, or supraclavicular
- Changes in inspiratory-expiratory ratio
- Production of sounds with respiration (eg, grunting, gurgling, stridor, rhonchi, rales, wheezes)
- Diaphoresis
- Decreased or absent breath sounds
- Presence of pale or cyanotic skin
- Presence of central cyanosis
- Alterations in mental status

nervous, or metabolic systems. It is also important to make an initial differentiation between upper and lower airway disease based on the presence or absence of stridor, rhonchi, rales, or wheezes on examination. Many common causes are listed in Box 70.1.

Evaluation

History

A brief history should be obtained while concomitant physical examination proceeds and initial treatment is begun (Box 70.4).

Physical Examination

Before a complete assessment can proceed, critical interventions that may change a child's clinical status should be undertaken. The child should be placed in a position of comfort if possible, and oxygen should be applied. Ventilation and oxygenation should be assessed. Nasal and/or oropharyngeal suctioning should be done if necessary.

Box 70.3. Comparison of Respiratory Systems in Children and Adults

- The head in children is proportionally larger and has less muscular support.
- The tongue in children is larger in relation to the mouth, is poorly controlled, and can cause airway obstruction.
- The airway diameter is smaller in children and collapses easily. Reductions in size resulting from secretions or inflammation cause greater resistance to air flow (resistance is proportional to $1/\text{radius}^4$).
- The larynx is higher and more anterior in children and the epiglottis is floppy, which makes visualization of the vocal cords more difficult.
- The narrowest part of the airway in children is at the cricoid ring, unlike in adults, in whom the narrowest point is at the vocal cords.
- The trachea in children is short. In newborns it is 4 cm long; in 18-month-old infants, 7 cm long; and in adults, 12 cm long.
- The major muscle of respiration in children is the diaphragm. Any interference with diaphragmatic motion in young children impedes respiratory function. Intercostal muscles are immature in children and fatigue easily.
- Children have less pulmonary reserve and higher metabolic demands.
- Normal respiratory rates are higher in children and vary by age.

Box 70.4. What to Ask

Respiratory Distress
- What was the onset of this problem like, and how has it progressed?
- For how long has it been occurring, and has a similar problem ever occurred before?
- Did the problem begin while the child was eating or playing?
- Has the child had any recent infections or fever?
- Are any members of the household ill?
- Is the child taking any medications?

Respiratory and heart rates should be determined for a period of at least 30 seconds. In the infant, abdominal excursions should be counted; in the older child, chest excursions should be counted. Respiratory rates in children are higher than in adults; infants may breathe 40 times per minute, 1-year-olds 25 times per minute, and 10-year-olds 18 times per minute (Table 70.1). These rates vary with age and changes of activity, emotion, and illness. Abnormal respiratory rates are defined as being faster than normal (ie, *tachypnea*), slower than normal (ie, *bradypnea*), or absent (ie, *apnea*). The neonate may exhibit periodic breathing, with periods of regular respirations alternating with irregular breathing. This is a normal variant for age. True apnea (ie, cessation of respiration) is accompanied by change in skin color or muscle tone and may be accompanied by bradycardia or altered level of consciousness.

The depth of respiration should be noted. Whether breaths are deep, gasping, or shallow should be determined. Rapid, shallow respirations may not provide enough inspiratory time for adequate gas exchange. The heart rate may also reflect respiratory compromise. Breath sounds should first be listened to in the axillae and then at the bases and apices. The absence of breath sounds may be an ominous sign. Children's breath sounds are usually well transmitted across the thorax because of the thin chest wall. It is common to hear upper airway noises when auscultating the lungs.

Abnormal sounds are caused by turbulent air passing through a narrowed airway. Resistance to flow through a hollow tube increases to the fourth power. Thus, the smaller the airway, the greater the resistance to flow generated by even small changes in the radius (as with edema, secretions, or foreign bodies). The nature of the sounds produced depends on the location of the narrowing in the airway. Gurgling, snoring, and stridor arise from the upper airway; rales, rhonchi, and wheezing arise from the lower airway. If no abnormal sounds are evident and breath sounds are absent or decreased, the upper or lower airways may be totally obstructed. *Grunting* is caused by turbulent air contacting a partially closed glottis. The child who grunts is generating partial obstruction of the upper airway and positive end-expiratory pressure to increase oxygenation.

The physician should also observe the effort the child expends in breathing. Increased work of breathing occurs when intercostal, subcostal, or supraclavicular retractions are present, the accessory muscles of respiration are used, breathing is abnormally noisy, or nasal flaring is seen. The normal work of breathing consumes 2% to 3% of total oxygen consumption. The increased work of breathing in the child with severe respiratory distress can potentially increase total oxygen consumption to 50%. Increased work of breathing can also be manifested by feeding difficulties and diaphoresis in infants and young children.

Additionally, the physician should observe the inspiratory-expiratory ratio while assessing the work of breathing. The ratio is approximately 1:1 in most patients. Prolonged expirations are most often noted with reactive airways disease.

Oxygen saturation should be measured by pulse oximetry in every child with respiratory symptoms. Levels below 93% while awake are indicative of significant hypoxemia.

Table 70.1. Vital Signs by Age

Age	Respiration (breaths/minute)	Pulse (beats/minute)	Systolic Blood Pressure (mm Hg)
Newborn	30–60	100–160	50–70
1–6 weeks	30–60	100–160	70–95
6 months	25–40	90–120	80–100
1 year	20–40	90–120	80–100
3 years	20–30	80–120	80–110
6 years	12–25	70–110	80–110
10 years	12–20	60–90	90–120

Laboratory Tests

Although the physical examination is the most important tool for assessing children in respiratory distress, laboratory tests such as respiratory viral and bacterial respiratory panels using polymerase chain reactions and other methodologies, complete and differential blood cell counts, and blood cultures may help in the diagnosis of infection. Point-of-care respiratory syncytial virus or influenza testing may also be beneficial during the peak seasons. It is important to note that meningitis, sepsis, and metabolic derangement may present with effortless tachypnea not associated with increased work of breathing. Arterial or venous blood gases may be beneficial in this situation; however, generally these should be reserved for patients in impending respiratory failure.

Peak expiratory flow or forced expiratory volume in 1-second determinations can be helpful in assessing the compliant older child with reactive airways disease. Oxygen saturation measurements can also be helpful in these children, because reduced levels (<100%) often correlate with the severity of disease.

Imaging Studies

Chest radiography can aid in assessing the child in respiratory distress, but such imaging should not be routinely obtained in patients with known reactive airways disease unless the child has a fever or is in status asthmaticus. Anteroposterior and lateral radiographs of the neck may also be beneficial in the patient with stridor. A patient with significant respiratory distress should not be moved from a monitored setting to the radiology suite; rather, portable radiographs should be obtained, if necessary.

Management

All infants and children in respiratory distress should be managed emergently. As stated previously, in such situations assessment and intervention often occur simultaneously. All children in respiratory distress should be reassessed frequently. Initially, the highest possible oxygen concentration should be delivered. Children who are able to maintain their own airway should never be forced to use an airway adjunct, because this may cause increased anxiety and distress. The patient with clear airways can be maintained with simple

interventions, such as oxygen blown by the face or given by mask or nasal prongs. Many patients with more severe croup, reactive airways disease, bronchiolitis, or pneumonia may benefit from noninvasive respiratory support, such as with continuous positive airway pressure or a heated humidified high-flow nasal cannula. More advanced airway management, such as bag-valve-mask ventilation or endotracheal intubation, may be necessary for the child who required assisted ventilation, airway protection, or hyperventilation.

Position

The child in respiratory distress who is alert and breathing spontaneously should be allowed to choose a position of comfort. Small infants who are incapable of positioning themselves are best placed upright with care taken not to flex or extend the neck. Children and their caregivers should be kept together to reduce anxiety.

The proper position for the unconscious child is the "sniffing position," with the neck slightly flexed and the head extended to open the airway. This can be facilitated by placing a towel under the occiput of the head or shoulders. If simple positioning does not relieve an obstruction, the airway should be opened using the chin lift or jaw thrust. If spinal trauma is a possibility, only the jaw thrust should be used. If this is unsuccessful, airway adjuncts, such as nasopharyngeal or oropharyngeal airways, can be placed to help prevent the soft tissue of the oropharynx from collapsing against the posterior pharyngeal wall.

Monitoring

All infants and children in respiratory distress should be carefully monitored. Pulse oximetry is helpful in determining the degree of oxygen saturation, and cardiac and respiratory monitoring provides constant readings of respirations and heart rate. Continuous end-tidal capnography may be beneficial in monitoring the patient with impending respiratory failure or the patient who requires ventilatory support. Frequent assessments of the patient are critical to ensure a good outcome.

Oxygen Administration

Oxygen should be delivered by the best method tolerated by the child. The 2 advantages of nasal prongs are that they are noninvasive and allow maintenance of a constant gas flow even when talking and eating. The concentration of oxygen delivered is limited, however, and irritation and drying of the mucous membranes may result.

Oxygen masks deliver a higher concentration of humidified oxygen than nasal prongs. Disadvantages include obstruction of the child's visual field, the potential for carbon dioxide retention, and anxiety because the face is covered. Various types of mask are available. The simple mask can deliver 30% to 60% oxygen concentration at flow rates of 6 to 10 L/min. Room air is drawn into the mask through the exhalation ports in the side of the mask. A non-rebreathing mask has valves that allow only oxygen (85%–95%) to flow from the reservoir bag to the patient on inhalation and additional valves on the exhalation ports of the mask that prevent entrapment of room air (Figure 70.1). The face tent is a soft plastic bucket shaped to the chin that is well tolerated by children (Figure 70.2). The face tent allows up to 40% oxygen to be delivered, and it has the advantage of allowing access to the face and mouth. A pocket mask is a small device that can be readily used in the office setting (Figure 70.3). A Venturi mask is rarely used in children but has the advantage of precisely titrating the oxygen concentration to be delivered from 24% to 60%.

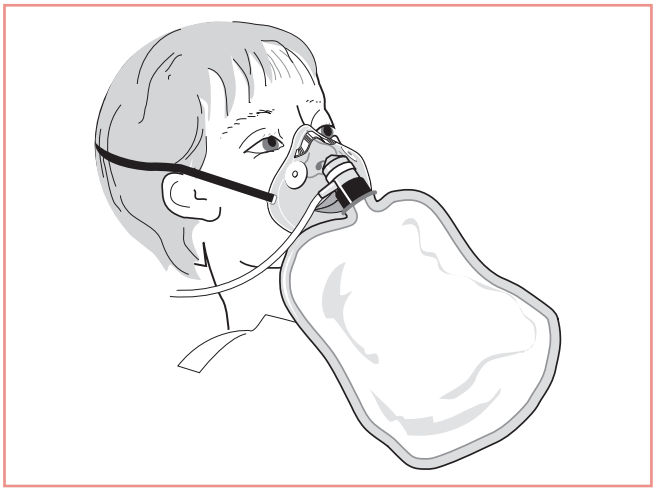

Figure 70.1. A non-rebreathing mask, which can deliver a high concentration of oxygen to a patient in respiratory distress.

Figure 70.2. Use of a face tent.

Noninvasive respiratory support, such as continuous positive airway pressure or heated humidified high-flow nasal cannula, is frequently used in patients with more significant disease or impending respiratory failure with excellent results. It decreases the work of breathing, increases oxygenation, and frequently serves as a bridge treatment while other agents are taking effect (eg, β agonists, steroids, antibiotics).

The child with respiratory failure requires assisted ventilation with a bag-valve-mask device or endotracheal intubation. A mask of the proper size should be used. The upper edge of the mask should fit snugly over the bridge of the nose without touching the eyes. The lower edge should rest directly on or just above the mandible. In the unconscious child, an oropharyngeal airway should

be inserted to prevent the tongue from obstructing the upper airway (Figure 70.4A). An appropriately sized oropharyngeal airway should reach from the patient's earlobe to the corner of the mouth. If the patient has an intact gag reflex, a nasopharyngeal airway may be inserted to achieve the same goal (Figure 70.4B). The nasopharyngeal airway is measured from the child's earlobe to the tip of the nostril. Endotracheal intubation is indicated in the child who requires control of the airway, needs airway protection, or requires hyperventilation.

Prognosis

Respiratory failure and resulting cardiopulmonary arrest are preventable in most infants and children if the condition is carefully assessed and appropriate critical interventions are implemented. Careful attention to ventilation and oxygenation usually results in a good outcome.

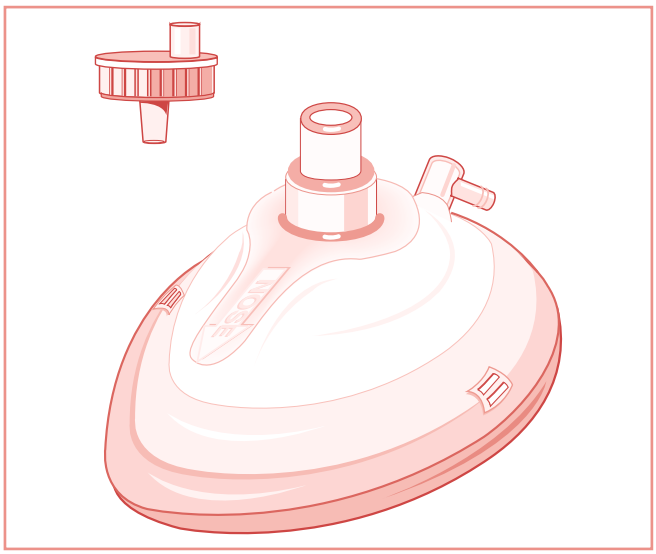

Figure 70.3. A pocket mask with a one-way valve and side oxygen port that can be used for assisted ventilation in the office setting.

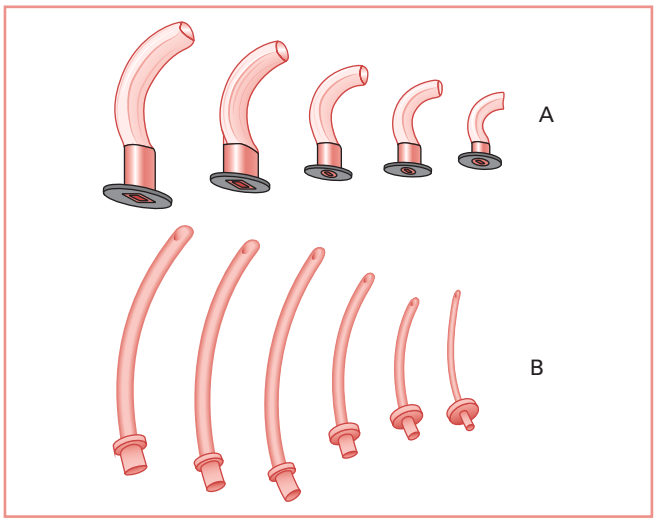

Figure 70.4. A, Oropharyngeal airways. B, Nasopharyngeal airways.

CASE RESOLUTION

The fussy infant has obvious signs of respiratory distress, including tachypnea, tachycardia, grunting, nasal flaring, and retractions. The differential diagnosis includes foreign body, infection (eg, croup, bronchiolitis), and reactive airways disease. The infant is placed in a position of comfort seated on his mother's lap and provided blow-by oxygen and a treatment with albuterol. A portable chest radiograph is obtained that shows mild hyperinflation but no infiltrate. His pulse oximetry reveals a level of 94%. A respiratory viral panel is obtained and the results reveal the presence of respiratory syncytial virus. The infant falls asleep, and his respiratory and heart rates return to normal. He is diagnosed with bronchiolitis and discharged home, and his mother is advised to return should he experience any further respiratory distress.

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CHAPTER 71

Stridor and Croup

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CASE STUDY

A 2-year-old boy has been breathing noisily for 1 day. For the past 3 days he has had a "cold," with a runny nose, fever (temperature up to 100.4°F [38°C]), and slight cough. The cough has gradually worsened and now has a barking quality.

On examination, the child is sitting up and has a respiratory rate of 48 breaths per minute with marked inspiratory stridor and an occasional barking cough. His other vital signs include an oxygen saturation of 95%, heart rate of 100 beats per minute, and temperature of 101.2°F (38.4°C). He has intercostal retractions, his breath sounds are slightly decreased bilaterally, and his skin is pale. The remainder of the examination is normal.

Questions

1. What is stridor?
2. What are the common causes of stridor?
3. What is the pathophysiology of viral croup?
4. How are children with croup managed?

Noisy breathing is a common symptom that often accompanies respiratory infections in children. The presence of stridor, a high-pitched crowing sound, often concerns children's caregivers. Some parents and guardians try home remedies to alleviate the symptoms, whereas many others immediately seek help in the office or emergency department setting. *Croup* is an inflammation of the larynx, trachea, and upper bronchioles (ie, laryngotracheobronchitis) that causes noisy breathing and stridor. It is among the most common causes of a seal-like barking cough and stridor in children.

Epidemiology

Croup most commonly affects children between 6 months and 3 years of age, generally in the fall or early winter. Children younger than 1 year account for 26% of cases. Infants are frequently more severely affected than older children. The condition is more common in boys than girls; two-thirds of all hospitalized children with croup are boys.

Stridor, which may be indicative of croup, may also be a sign of epiglottitis. The incidence of epiglottitis in children has dramatically decreased since 1988 following the development and widespread use of the vaccine against *Haemophilus influenzae* type b. Many young children may be incompletely immunized, and other bacteria exist that may cause epiglottitis; thus, epiglottitis should still be considered in toxic-appearing children with rapid onset of symptoms of upper airway obstruction. Before *Haemophilus influenzae* type b immunization, the ratio of cases of epiglottitis to croup was 1:100. Currently, epiglottitis in children is exceedingly rare.

Clinical Presentation

Viral Croup

Viral croup commonly begins with 2 to 3 days of viral upper respiratory symptoms (eg, rhinorrhea, sore throat, cough) and a generally low-grade fever. Higher-grade fevers may occur depending on the causative agent. At day 3 or 4, the characteristic signs of a hoarse voice, barking cough, and inspiratory stridor manifest. This frequently occurs suddenly and often at night. Symptoms worsen in the next 1 to 2 days and then resolve over the next several days.

Spasmodic Croup

Spasmodic croup typically occurs in children 2 to 5 years of age and often presents suddenly, commonly at night, without the previous complaint of upper respiratory symptoms. As in viral croup, hoarseness, barking cough, and stridor occur; however, these symptoms generally are less severe in spasmodic croup. The condition frequently resolves completely when affected children are exposed to cool or humified air. It may be recurrent. Some children may have the prodrome of a viral upper respiratory syndrome. Fever is uncommon. The etiology is unknown but is likely a reaction to a viral infection or an allergic phenomenon. A family history of recurrent stridor in children with spasmodic croup may exist.

Bacterial Tracheitis

The classic presentation of bacterial tracheitis is of a school-age child presenting with a prodrome of an upper respiratory infection. After a few days, this is followed by the abrupt progression to toxic appearance. A high fever, productive cough, inspiratory stridor, and tachypnea with moderate to severe respiratory distress commonly occur.

This generally occurs as the airway becomes secondarily infected with staphylococcal or streptococcal species. White blood cell counts are frequently significantly elevated. Abrupt decompensation may occur as pseudomembranes loosen and obstruct the airway.

Epiglottitis

Whereas acute bacterial epiglottitis was classically seen in young children, currently it is more common in adolescents and young adults. Historically, it presented with the abrupt onset of toxic appearance, high fever, sore throat, odynophagia, and muffled voice. Rapid progression followed with severe respiratory distress, drooling, stridor, tripod positioning, and frequent airway obstruction. Modern presentations are commonly less severe or progressive because of the change in pathogens. Sore throat, odynophagia, muffled voice, and significant tenderness to palpitation of the larynx frequently occur, but currently, toxic appearance and progression to airway obstruction are uncommon.

Foreign Body

Laryngotracheal foreign body aspiration may occur as a witnessed event. Choking, coughing, gasping, and stridor frequently occur, and the patient may present with these symptoms or they may have resolved by the time the patient is seen in the doctor's office. Presenting symptoms of foreign bodies in the lower larynx include dysphagia, gagging, and throat discomfort. Presenting symptoms of foreign bodies in the trachea include coughing, wheezing, and, with time, pneumonia.

Pathophysiology

Stridor

Stridor is generally caused by partial obstruction of the airway between the nose and larger bronchi. Obstruction at the level of the nose or pharynx may produce snoring or gurgling sounds. Turbulent airflow in the laryngeal area or upper trachea causes the high-pitched crowing sound characteristic of stridor. Edema and inflammation at the vocal cords and subglottic areas result in inspiratory stridor, whereas obstruction below the cricoid cartilage may cause inspiratory and expiratory stridor. Some of the more common causes of stridor are listed in Box 71.1.

The sounds produced at various levels of obstruction can give the primary care physician clues about the etiology of the problem. The most common cause of stridor that begins shortly after birth is tracheomalacia, a condition secondary to the immaturity of the cartilage of the trachea. Laryngomalacia, which is caused by floppy supraglottic structures, resolves after several months.

The upper airway of infants and children is more susceptible to obstruction as the result of anatomic differences between children and adults. The tongues of children are relatively large, and the epiglottis is floppy and shaped somewhat like the Greek letter omega (Ω). The angle between the epiglottis and glottis is more acute in children, which makes direct visualization of the airway more difficult than in adults. Cartilaginous structures are less rigid in infants. During inspiration, negative intraluminal pressure is generated below the level of obstruction, which causes narrowing of the airway and turbulence of the airflow. This occurs more often in children than adults because the tracheal rings are not well formed. Additionally, the smaller size of the airway in children makes resistance to airflow greater when obstruction is present.

Resistance increases exponentially, so the smaller the airway the greater the resistance to flow. Alterations in the diameter of the airway are most often caused by edema and inflammation. Stridor may also occur from a variety of conditions, including congenital anomalies, infection, allergic and anaphylactic reactions, cysts, tumors, and trauma. Even small localized areas of airway narrowing in infants and children can cause respiratory distress.

Box 71.1. Causes of Stridor

Congenital Anomalies
- Choanal atresia
- Laryngeal web
- Laryngocele
- Laryngomalacia
- Macroglossia (Beckwith syndrome)
- Subglottic stenosis
- Tracheal web or cyst
- Tracheomalacia
- Vascular ring

Inflammatory/Infectious Lesions
- Abscess (ie, retropharyngeal, peritonsillar, parapharyngeal)
- Angioedema
- Bronchitis
- Diphtheria
- Epiglottitis
- Infectious mononucleosis
- Severe tonsillitis
- Tracheitis
- Viral croup

Trauma
- Direct trauma to the upper airway
- Postintubation subglottic stenosis

Neurogenic
- Laryngeal paralysis
- Poor pharyngeal muscle tone

Caustic or Thermal Injury
- Hot gas or liquid
- Lye or caustic ingestion

Foreign Body
- Neoplasm

Croup

Croup is most often caused by an infection with parainfluenza virus (type 1 or 2). Several other causes include respiratory syncytial virus, influenza virus A or B, adenovirus, rhinovirus, coxsackievirus,

measles, and herpes simplex virus infections. Metapneumovirus and novel coronavirus, which more commonly cause bronchiolitis, have also been implicated. Simultaneous infections with more than 1 virus are common. Particularly severe disease may be associated with influenza A, respiratory syncytial virus, or adenovirus infection. Infection occurs via respiratory droplets spread from other infected individuals.

The virus first attacks the nasopharynx and subsequently spreads to the larynx and upper trachea. The infection causes inflammation and edema of the airway that often involves the vocal cords and subglottic areas, producing the typical barking cough, hoarseness, and inspiratory stridor. Uncommonly, in severe cases, the lower airways also may be involved, resulting in impaired alveolar ventilation and wheezing. In some children, secondary bacterial superinfection may rarely occur with bacterial tracheitis or extension of infection to the lower airway producing pneumonia. Airways of infants are small and particularly susceptible to obstruction because of the narrow subglottic region and laxity of the cartilaginous structures.

Differential Diagnosis

The differential diagnosis of stridor is presented in Table 71.1.

Evaluation

History

A complete history should be obtained (Box 71.2).

Physical Examination

It is important to assess the degree of respiratory distress and place children in a position of comfort; monitor heart rate, ventilation, and oxygenation; deliver oxygen; and suction the nasopharynx if necessary (see Chapter 70). The stridorous sounds produced are usually inspiratory but may be inspiratory and expiratory if the disease progresses to the lower airway. The presence of stridor at rest or with sleep should be assessed as well as the severity of retractions with breathing. Breath sounds may be decreased bilaterally, and severe tachypnea, with respiratory rates from 40 to 80 breaths per minute, may occur. Peripheral or central cyanosis and alterations in mental status associated with severe disease should be noted. Assessment of croup severity may be helpful to direct initial therapy in mild, moderate, or severe cases as well as monitor response to treatment and predict disposition (Table 71.2).

Laboratory Tests

Investigations, such as a complete blood cell count and cultures, are rarely helpful unless the physician is concerned about secondary bacterial infection. The white blood cell count may be normal or mildly elevated, and the differential count may show a predominance of polymorphonuclear cells. Polymerase chain reaction viral and bacterial respiratory panels may be helpful in more severely ill or admitted patients.

Imaging Studies

Radiographs of the soft tissues of the upper airway are sometimes helpful. In children with croup, the classic steeple sign of the subglottic area where the airway narrows like a church steeple or pencil tip is demonstrated on the frontal view. A lateral neck radiograph may reveal ballooning of the hypopharynx, a normal epiglottis, and a normal retropharyngeal space (Figure 71.1). Radiography is not recommended with a classic presentation of croup. Thickening of the epiglottis, which appears thumbprint-shaped, and obliteration of the vallecular space may be seen on

Table 71.1. Differential Diagnosis of Stridor

Factor	*Viral Croup (Age 3–36 Months)*	*Spasmodic Croup (Age 3–36 Months)*	*Bacterial Tracheitis (Age 1–10 Years)*	*Epiglottitis (Age 1–8 Years)*	*Foreign Body (All Ages)*
Prodrome	Upper respiratory infection symptoms; onset over 2–5 days	None; sudden onset at night	Upper respiratory infection symptoms for days, followed by rapid-onset fever and respiratory distress	Usually none; rapid onset over several hours	None; sudden onset
Fever	Low grade	None	Low grade initially, then higher	Usually temperature above 102.2°F (39°C)	None
Cough	Barking	Barking	Dry initially, then barking	None or dry	May or may not be present
Respiratory distress	Present	Present	Absent or mild initially, then severe	Present and severe	Usually present
White blood cell count	Normal or slightly elevated	Normal	Normal initially, then elevated	Elevated	Normal
Blood culture	No growth	No growth	Growth uncommon	*Haemophilus influenzae*	No growth
Radiograph	Subglottic narrowing; steeple sign	Subglottic narrowing may or may not be present	Subglottic narrowing; steeple sign and ragged trachea	Swollen epiglottis	Air trapping; may demonstrate a foreign body

Box 71.2. What to Ask

Stridor and Croup

- Did the child have an antecedent respiratory infection?
- Does the child have a fever? If so, how high is the temperature?
- Was the onset of stridor abrupt?
- Is there stridor at rest/sleep or only with agitation?
- Has the child had stridor previously?
- Does the child have any ill contacts?
- Does the child have any associated symptoms, such as vomiting, diarrhea, or rash?
- Is the child feeding normally?
- Is the child drooling?

lateral neck radiographs in patients with epiglottitis. Widening of the retropharyngeal space dorsal to the tracheal air column may be seen with retropharyngeal abscess. Children with respiratory compromise should be evaluated in the emergency department with portable X-ray equipment.

Direct visualization or imaging studies (eg, barium swallow, computed tomography of the neck or thorax) are helpful in diagnosing congenital anomalies (eg, vascular ring) in atypical or recurrent cases.

Management

Most children with croup and stridor can be managed as outpatients. Caregivers should be given careful instructions so that they understand the course of the illness, know what to expect, and realize when emergency care is needed. Children with a prolonged or recurrent history of stridor may require consultation with a head and neck specialist. If a specific cause of stridor is identified, such as a foreign body, appropriate management should be instituted.

Children with croup should be treated with gentleness and should not be upset. They should remain with their caregivers and be allowed to assume a position of comfort. Agitation and crying increase respiratory distress and oxygen demand. Procedures should be kept to a minimum. The heart rate, respiratory status, and oxygen saturation should be continuously monitored while the patient is being treated and observed. Airway adjuncts that increase agitation should not be used.

Historically, cool mist has been provided by blow-by or mask. Humidified oxygen or air, which is thought to decrease the viscosity of secretions and reduce airway edema, had long been the mainstay of therapy for croup. Several randomized, controlled trials have questioned this practice, however, demonstrating no benefit of cool humidified mist therapy. Consensus statements now reflect this finding, and most physicians have abandoned this treatment practice. Symptoms of spasmodic croup usually resolve within 6 hours of the onset without treatment; however, cool, humidified mist is still often used as the sole therapy for this disorder.

Currently, treatment of croup with corticosteroids is the mainstay of therapy, and its use is less controversial than the use of cool mist. Several studies have demonstrated that dexamethasone given as a single dose of 0.6 mg/kg is effective in shortening the course and severity of mild, moderate, and severe croup if given in the first 3 days. Several smaller randomized trials have also suggested that one-half the dose of dexamethasone may be equally effective, with fewer adverse effects in patients with mild or moderate croup. Dexamethasone should be given orally but may be given

Table 71.2. Clinical Assessment of Croup Severity

Sign or Symptom	*Normal*	*Mild*	*Moderate*	*Severe*
Air entry	Normal	Mild decrease	Moderate decrease	Marked decrease
Color	Normal	Normal	Cyanotic if agitated	Cyanotic at rest
Level of consciousness	Normal	Restless when disturbed	Restless when undisturbed	Lethargic
Retraction	None	Mild	Moderate	Severe
Stridor	None	Only with agitation	Moderate at rest	Severe at rest
Disease Categories				
Degree	*Management*			
Mild	Dexamethasone 0.3–0.6 mg/kg orally Outpatient observation			
Mild to moderate	Dexamethasone 0.3–0.6 mg/kg orally; consider racemic epinephrine If child improves after observation, is >6 months of age, and has a reliable family, outpatient observation			
Moderate	Dexamethasone 0.6 mg/kg orally or intramuscularly; racemic epinephrine and hospital admission			
Severe	Racemic epinephrine, dexamethasone 0.6 mg/kg orally or intramuscularly, oxygen, and admission to intensive care unit			

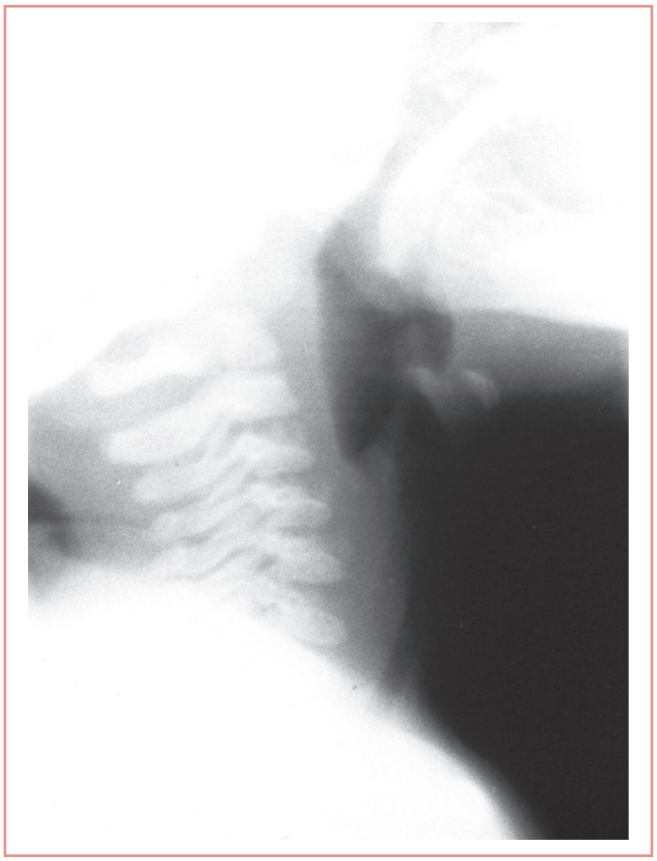

Figure 71.1. Lateral neck radiograph of viral croup. Note the ballooning of the hypopharynx and narrowing in the subglottic area.
Courtesy of Dr J. S. Seidel, Division of General and Emergency Pediatrics, Harbor-UCLA Medical Center, West Carson, California.

as an intramuscular or intravenous injection for children who are unable to take oral medication or have persistent emesis. Use of the tablet preparation ground up in applesauce is often recommended, because the liquid preparation does not taste good and is not well tolerated. Recent studies using nebulized budesonide also demonstrate the same efficacy in reducing respiratory distress and decreasing croup severity but at higher cost. Continuous or long-term therapy with steroids does not seem to alter the clinical course of the disease or the period of hospitalization and is not recommended. Treatment with antibiotics is not indicated unless infection with bacteria is evident.

Use of racemic epinephrine has also become less controversial. Several older studies have shown that there was no difference in the long-term outcome between children who were treated with epinephrine and those who received a placebo. More recent and robust studies have clearly demonstrated clinical benefit of the drug when given via nebulizer. This effect lasts a few hours, and repeat doses of the drug may be needed until the anti-inflammatory properties of the administered steroids show clinical effect. Thus, if racemic epinephrine is used on patients who are going to be discharged, it is prudent to observe them for 3 to 4 hours after treatment for return or worsening of stridor. The anti-inflammatory effects of dexamethasone take several hours for onset, and racemic epinephrine may have significant bridging effects in reducing symptoms during this period.

Hospitalization is required for less than 10% of patients presenting to the emergency department. It should be considered for children with an oxygen requirement, who are in moderate to severe respiratory distress, with significant stridor at rest, who are unable to eat, or whose parents are unable to cope with the tasks required to manage the child at home. It is always indicated for children with a bacterial infection, such as epiglottitis or tracheitis.

Studies are ongoing, but early results suggest that continuous positive airway pressure and heated humidified high-flow nasal cannula noninvasive ventilation significantly improve croup symptoms, decrease the work of breathing, and reduce the rates of respiratory failure and need for invasive ventilation in many patients. Use of either therapy use should be considered in most hospitalized patients.

With early steroid administration, racemic epinephrine use, and noninvasive ventilatory support only approximately 1% of infants and children with croup require controlled ventilation with endotracheal intubation. Indications for intubation include severe respiratory distress, altered mental status, hypoxia, and hypercapnia. A major complication of endotracheal intubation in children with croup is subglottic stenosis, which occurs because the endotracheal tube may traumatize the inflamed airway, resulting in permanent damage. Patients should be extubated as soon as possible.

Direct laryngoscopy may be necessary in some children in whom the etiology of stridor is not clear. This procedure should be done by a physician who is experienced in managing the airway.

Prognosis

Stridor is a serious sign indicative of upper airway obstruction and potential respiratory compromise. Although it has many causes, the prognosis typically is determined by the rapidity of diagnosis and institution of appropriate therapeutic measures, particularly stabilizing the patient and ensuring patency of the airway. Certain conditions, such as croup, often resolve spontaneously within a few days, although some children require hospitalization and, rarely, assisted ventilation. Other conditions, such as foreign bodies or tumors, necessitate aggressive intervention to prevent death resulting from airway obstruction.

CASE RESOLUTION

The 2-year-old with the antecedent infection and stridor has the classic signs of mild to moderate croup. Initially, adequate ventilation, oxygenation, and circulation should be ensured. Following this, other diagnostic studies and specific therapy can be considered, such as nasal suctioning, dexamethasone, and racemic epinephrine. A period of posttreatment observation is warranted. If his condition improves, close outpatient management may be considered.

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CHAPTER 72

Sudden Unexpected Infant Death and Brief Resolved Unexplained Events

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CASE STUDY

A 4-month-old boy is brought to the emergency department by paramedics after being found blue and not breathing by his mother. He had previously been well except for a mild upper respiratory infection. His mother fed him at 2:00 am and found him blue and lifeless lying next to her in bed at 6:00 am. Although the mother smoked cigarettes during pregnancy, the pregnancy and delivery were otherwise normal. The infant received the appropriate immunizations at 2 months of age.

Questions

1. What factors are associated with sudden unexpected infant death?
2. What is the relationship between sudden infant death syndrome and sudden unexpected infant death?
3. What should parents be advised to help prevent sudden unexpected infant death?
4. What is the appropriate evaluation of the infant who presents with a brief resolved unexplained event?
5. Why are sudden unexpected infant death and brief resolved unexplained events not related?
6. What services are available to families whose infant has died from sudden unexpected infant death?

Sudden unexpected infant death (SUID) refers to all sudden, unexpected death in infants younger than 1 year. *Sudden infant death syndrome* (SIDS), a subcategory of SUID, is a diagnosis of exclusion following the death of a previously healthy infant younger than 1 year in which no contributing factors are identified (including the absence of an unsafe sleep environment) after obtaining a comprehensive medical history of the infant and family and performing a thorough postmortem examination and death scene investigation. In the United States, SUID is the most common cause of death in children younger than 1 year (excluding the neonatal period); in most cases, a contributory factor is present, such as an unsafe sleep environment.

A *brief resolved unexplained event* (BRUE) is a sudden, brief, and resolved event that occurs in an infant younger than 1 year of age and that involves at least 1 of the following findings: cyanosis or pallor; decreased, absent, or irregular breathing; change in tone; or decreased responsiveness. What is now known as BRUE was formerly termed an "apparent life-threatening event" (ALTE). For historical reasons, BRUE and SUID are discussed in this chapter because ALTE and SIDS were once thought to be related. A BRUE is not a risk factor for SUID, however.

Sudden Unexpected Infant Death

Epidemiology and Risk Factors

Sudden unexpected infant death accounts for 3,000 to 4,000 infant deaths per year in the United States, with an overall incidence of 0.93 per 1,000 live births. These figures were dramatically higher before the Safe to Sleep campaign (originally the Back to Sleep campaign) promoted by the American Academy of Pediatrics (AAP) to place babies in the supine position for sleep. Before the institution of this campaign, the annual death rate from what was then termed SIDS was approximately 5,000 to 8,000, with an incidence of approximately 1.4 per 1,000 live births.

Sudden unexpected infant death more commonly affects boys than girls and occurs more often in the winter months. The peak incidence of SUID occurs at 2 to 3 months of age, with 90% of deaths occurring before age 6 months.

The frequency of SUID differs in different populations in the United States and other countries. Although the incidence of SUID is decreasing among all groups, the rates in black and American Indian/Alaska Native children is 2 to 3 times the national average. One factor contributing to the higher rate of SUID is the increased

incidence of nonsupine sleeping in black infants. In 2001, the prevalence of prone positioning was 11% for white infants and 15% to 21% for black infants.

Clinical Presentation

Patients with SUID present in cardiopulmonary arrest, with a history of previous good health or antecedent upper respiratory infection. They often present in the early morning hours, having succumbed during sleep. The physician cannot determine the cause of death of the deceased infant; that is the role of the coroner.

Pathophysiology and Risk Factors

Numerous epidemiologic, maternal, and infant factors have been associated with SUID, including preterm birth and intrauterine growth restriction (Box 72.1). Mothers of children with SUID are frequently young and unmarried, smoke cigarettes, and have had fewer than recommended doctor visits during the prenatal and postpartum periods. Parental alcohol use is also a risk factor for SUID. In 1 study SUID rates were 33% higher on New Year's Day than any other day, which suggests that parents under the influence of alcohol are less able to monitor their infants safely. Despite initial reports and significant research efforts, no data have established a causal relationship of BRUEs, apnea, immunizations, or repeated episodes of cyanosis with SUID.

Although bedsharing was once promoted to enhance breastfeeding, accidental suffocation and SUID are associated with this practice. The importance of a safe sleep environment is underscored by a study published in 2000 in which the authors investigated 119 SUID cases over a 4-year period following the initiation of the Back to Sleep campaign. In only 8.4% of these SUID cases was the infant found in a nonprone position, alone in their bed and without any potential obstructions of the external airway by bedding.

Pediatricians play a critical role in counselling parents about safe sleep practices. One study reported that 11% of new mothers reported "usually" bedsharing, yet only 36% of parents had a conversation about bedsharing with their pediatrician. If their pediatrician had a negative view of bedsharing, parents were less likely to bedshare. If the pediatrician had a neutral view, parents were more likely to bedshare. Because approximately 20% of SUID cases in the United States occur while in the care of someone other than the parent, secondary caregivers and staff at child care centers also should be educated about the critical need for babies to sleep on their backs and in a sleep space free of blankets, pillows, and other objects that may obstruct an infant's airway.

Box 72.1. Factors Associated With Sudden Unexplained Infant Death

- Sleeping in prone or side-lying position
- Soft bedding
- Overheating
- Bedsharing
- Socioeconomic disadvantage
- Maternal smoking
- Preterm birth
- Male sex
- Maternal youth
- Low birth weight
- Poor prenatal care
- Family previously reported to child protective services

In addition to exposure to the environmental factors that increase an infant's risk for SUID, most theories suggest the existence of an underlying vulnerability in those who experience SUID. The brainstems of infants who died of SUID have significantly lower concentrations of serotonin and tryptophan hydroxylase, a biosynthetic enzyme of serotonin; higher serotonergic neuron counts; decreased serotonin 1A receptor binding; and reduced serotonin transporter binding in the medulla. Furthermore, several studies have shown a significant increase in monoamine oxidase A (MAO-A) gene polymorphisms that could cause overexpression of MAO-A. These findings suggest that abnormalities in serotonin synthesis, release, and clearance impair the infant's ability to appropriately regulate arousal and respiratory drive in response to potential life-threatening challenges during sleep.

Numerous other associations with SUID have been reported, including altered polymorphisms of proinflammatory cytokines, abnormalities in other neurotransmitters, small mandibular size, disorders of fatty acid oxidation, and cardiac channelopathies, including long QT syndrome. The AAP does not currently recommend universal electrocardiography (ECG) screening at birth to identify potential SUID patients, however, although ECG has been recommended for infants with abnormal hearing screening because of the association of hearing deficits with long QT syndrome. Additionally, pulse oximetry in the newborn period may help identify infants with occult congenital heart disease.

The association between SUID and fatal child abuse has also received attention, although infanticide is estimated to be the cause in less than 5% of suspected SUID cases. The evaluation of the home environment of infants who have died from SUID, referred to as *death scene investigations*, may reveal factors that contributed to the death of some of these infants. Unsafe sleeping environments (eg, sofas) and parental drug paraphernalia may identify such factors. A complete postmortem examination may reveal prior or recent trauma. An autopsy should include an assessment for long bone fractures as well as intracranial hemorrhage, although these findings may account only for the existence of prior trauma rather than for the infant's death. In some municipalities, child fatality boards review each case of reputed SUID to assess whether an etiology can be determined. Infants who are targets of medical child abuse may present with SUID or BRUE. Such infants are suffocated by the parents until they become apneic or die. Because distinguishing between SUID and intentional suffocation is quite difficult pathologically, the AAP Committee on Child Abuse and Neglect has cited factors that should heighten the physician's suspicion for possible child abuse (Box 72.2). The use of in-hospital covert video surveillance has facilitated the recognition of apnea secondary to medical child abuse.

Box 72.2. Circumstances in Which the Physician Should Be Alert to the Possibility of Child Abuse

- Previous recurrent cyanosis, apnea, or brief resolved unexplained event while in the care of the same person
- Previous unexpected or unexplained death of 1 or more siblings
- Simultaneous or near-simultaneous deaths of twins
- Death of other infants while cared for by the same unrelated person
- Blood on the infant's nose or mouth prior to cardiopulmonary resuscitation
- Infant older than 6 months

Management

In most jurisdictions, cases of SUID must be reported to the coroner's office. The AAP recommends a prompt death scene investigation; appropriate use of available medical specialists by medical examiners and coroners, including pediatricians; and a postmortem examination within 24 hours of death, including radiologic skeletal surveys and toxicology and metabolic screening. A complete review of the medical records of the patient is essential. A timely information session with parents is recommended when the results of the investigation determine SUID or another cause of death.

Physicians must provide care to families whose infant has succumbed to SUID. Parents should be guided through issues such as planning the funeral and ending lactation when appropriate. For ongoing support, parents should be referred to groups and agencies to help them cope with the unexpected loss of their child. Information about these organizations can be obtained from First Candle (1-800-221-7437; www.firstcandle.org).

Prevention

Prevention of SUID has become a focus of public health measures, including promotion of smoking cessation and access to prenatal care. Parents must be instructed to avoid soft bedding for their infant, bedsharing, placing their infant on a sofa for sleep, and overheating, and they should be instructed to place their infant in the supine position in a crib. See Box 72.3 for additional recommendations.

Pacifier use has been associated with a decreased incidence of SUID. The AAP recommends that caregivers consider offering a pacifier at naptime and bedtime through age 12 months. The pacifier should not be reinserted after the infant falls asleep or coated in any sweet solution. The pacifier should be cleaned often and replaced regularly. For infants fed mother's milk, pacifier introduction should be delayed until breastfeeding is well established.

The AAP recommends only the supine sleep position, because side sleeping increases the risk of SUID 2-fold relative to back sleeping. A firm crib mattress covered by a fitted sheet is the recommended sleep surface for infants. Soft bedding, such as water beds and couches, or objects in the sleep environment, such as stuffed toys, pillows, quilts, and comforters, are not safe.

Box 72.3. American Academy of Pediatrics Recommendations to Reduce the Risk of Sudden Unexpected Infant Death

- Back to sleep for every sleep.
- Use a firm sleep surface.
- Breastfeeding is recommended.
- Room-sharing with the infant on a separate sleep surface is recommended.
- Keep soft objects and loose bedding away from the infant's sleep area.
- Consider offering a pacifier at naptime and bedtime.
- Avoid smoke exposure during pregnancy and after birth.
- Avoid alcohol and illicit drug use during pregnancy and after birth.
- Avoid overheating.
- Pregnant women should seek and obtain regular prenatal care.
- Infants should be immunized in accordance with American Academy of Pediatrics and Centers for Disease Control and Prevention recommendations.
- Do not use home cardiorespiratory monitors as a strategy to reduce the risk of SIDS.
- Health care providers, staff in newborn nurseries and neonatal intensive care units, and child care providers should endorse and model the SIDS risk-reduction recommendations from birth.
- Media and manufacturers should follow safe sleep guidelines in their messaging and advertising.
- Continue the "Safe to Sleep" campaign, focusing on ways to reduce the risk of all sleep-related infant deaths, including SIDS, suffocation, and other unintentional deaths. Pediatricians and other primary care providers should actively participate in this campaign.
- Avoid the use of commercial devices that are inconsistent with safe sleep recommendations.
- Supervised, awake tummy time is recommended to facilitate development and to minimize development of positional plagiocephaly.
- Continue research and surveillance on the risk factors, causes, and pathophysiologic mechanisms of SIDS and other sleep-related infant deaths, with the ultimate goal of eliminating these deaths entirely.
- There is no evidence to recommend swaddling as a strategy to reduce the risk of SIDS.

Abbreviation: SIDS, sudden infant death syndrome.

Adapted with permission from American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. SIDS and other sleep-related infant deaths: updated 2016 recommendations for a safe infant sleeping environment. *Pediatrics*. 2016;138(5):e20162938.

The AAP recommends that parents sleep in a separate but proximate sleeping environment from their infant (ie, room-sharing but not bedsharing). Dressing babies in light clothing during sleep and maintaining the room temperature at a comfortable level for adults is recommended to avoid overheating.

During the first weeks of hospitalization, preterm newborns are often placed in a nonsupine position because of respiratory complications and gastroesophageal reflux. The newborns become accustomed to this position, and the parents learn from the modeling of the hospital staff to place them in this unsafe position. The AAP

Task Force on Sudden Infant Death Syndrome encourages neonatologists and nurses to begin placing preterm newborns on their backs "significantly before the infant's anticipated discharge."

One unintended consequence of supine sleep is the increased incidence of positional plagiocephaly. To minimize the risk for head deformities and foster appropriate motor development, parents and caregivers are encouraged to vary the head position at sleep times, avoid swing and bouncy seats that increase pressure on the back of the head, and encourage adult-observed tummy time during waking hours starting from birth. The pediatrician can suggest tummy time at daytime diaper changes, even if for only 1 or 2 minutes.

Brief Resolved Unexplained Events

Epidemiology

Because BRUE is a relatively new term, studies are needed to gather epidemiologic data. The rates for ALTEs, the term previously used for many BRUEs, varied between 0.6 and 2.46 per 1,000 live births. The rates of BRUE likely are lower because unlike with an ALTE, after a cause for a BRUE is established the event is no longer classified as a BRUE; instead, it is then classified by the condition that precipitated the event.

Clinical Presentation

The infant who has experienced a BRUE at home appears well without any need for medical intervention but has a highly variable history in terms of whether resuscitation was required, length of the episode, and associated symptoms. An infant who is ill-appearing on presentation by definition does not have a resolved event and requires immediate intervention and further workup. Patients with BRUE often present between the hours of 8:00 am and 8:00 pm—a time of day different from the typical early morning hours for an SUID.

Differential Diagnosis

The major challenge for physicians is to evaluate infants who have experienced a BRUE and determine if any underlying condition caused the episode (Box 72.4). In most cases, no etiology for a BRUE is established, and the episode represents an isolated event. If an etiology is found, by definition the event is no longer unexplained, and the discharge diagnosis should reflect the etiology.

Evaluation

History

The history may provide the clue to the etiology of BRUE (Box 72.4).

Physical Examination

A complete physical examination should be conducted. If the infant is floppy, has poor color, or has required mouth-to-mouth resuscitation or vigorous stimulation, the event is not considered a BRUE because the symptoms are not resolved. The physician should check for the presence of bruising, retinal hemorrhage, dysmorphic features, growth impairment, and abnormal neurologic or developmental findings, which may suggest an alternative etiology (Box 72.5). The presence of tachypnea, retractions, wheezing, or cough is consistent with a respiratory infection, such as respiratory syncytial virus or pertussis. After an etiology for the BRUE is determined (eg, respiratory syncytial virus), the diagnosis of BRUE should be changed to reflect the etiology.

Box 72.4. What to Ask

Brief Resolved Unexplained Event

- What were the events leading up to the episode?
- Was the infant awake and eating? (Consider gastroesophageal reflux.)
- Was the infant awake, and did the eyes roll back or the body stiffen or jerk? (Consider a seizure.)
- How serious was the event? Did breathing resume spontaneously, or was it necessary to initiate cardiopulmonary resuscitation?
- Have similar events occurred in the past?
- Is the infant well? Has the infant been ill recently?
- Has the infant had respiratory symptoms, such as wheezing or cough?
- Was the infant given an over-the-counter cough and cold product?
- Do siblings have a history of sudden unexpected infant death or brief resolved unexplained event that would suggest the presence of a familial disorder or child abuse?
- Were there any problems with the pregnancy or delivery?

Box 72.5. Brief Resolved Unexplained Events: Alternative Diagnoses to Consider

- Gastroesophageal reflux or overfeeding
- Lower respiratory tract infection
- Sepsis
- Pertussis
- Respiratory syncytial virus
- Infantile botulism
- Seizure
- Incorrect medication dose or overdose
- Inborn errors of metabolism
- Child abuse
- Intracranial hemorrhage
- Airway anomaly
- Aspiration
- Breath-holding spell
- Cardiac arrhythmia/anomaly

Risk Stratification

Before publication of the current guidelines, it was common to admit all infants with BRUE for observation, workup, and monitoring. The 2016 AAP guidelines identify a low-risk subset of patients who require a much more limited evaluation without laboratory testing (Box 72.6).

Management

The management of BRUE depends on whether the BRUE is classified as low- or high-risk. Guidelines for management of BRUE are

Box 72.6. Patients at Low Risk for Brief Resolved Unexplained Event

- Age >60 days
- Born ≥32 weeks' gestational age and corrected gestational age ≥45 weeks
- No cardiopulmonary resuscitation by a trained medical provider
- Event duration <1 minute
- First event
- No concerns on history and physical examination (eg, no family history of sudden cardiac death)

detailed in this section, and a treatment algorithm is provided in Figure 72.1.

Low-Risk Brief Resolved Unexplained Event

The patient may be observed briefly (ie, for 1–4 hours) with serial examinations with or without pulse oximetry. Pertussis testing may be considered, especially in the setting of exposure or unvaccinated caregivers. If a diagnosis of pertussis is likely, the patient typically is observed and started on empiric antibiotics pending results.

Although arrhythmia is rare, an ECG may be indicated because it is a noninvasive test with high negative predictive value. Syncope is associated with future sudden cardiac death in patients with long QT syndrome. Other channelopathies, Wolff-Parkinson-White syndrome, and cardiomyopathy or myocarditis also can be detected on ECG.

In general, the low-risk infant who experienced a BRUE and does not have an identifiable precipitating condition may be discharged from the emergency department after a brief observation of 1 to 4 hours. Prior to discharge from the hospital, the parent or caregiver of the infant who experienced a BRUE should receive resources for cardiopulmonary resuscitation training, be educated about BRUE, and be counseled to arrange close follow-up care. The previous guidelines for ALTEs advised eliminating tobacco smoke exposure, which is not explicitly addressed in the BRUE guidelines. However, given the overall health risks of secondhand smoke exposure, the physician should use every opportunity to counsel caregivers on smoking cessation.

Historically, home apnea monitoring was prescribed for the newborn at risk for apnea. Based on a plethora of studies, the AAP does not recommend home apnea monitors for the prevention of SUID. Home apnea monitoring may be considered for the preterm newborn or infant at risk for repeated episodes of apnea of prematurity on discharge from the hospital. Discontinuation of such monitoring at approximately 43 weeks' gestational age should be considered.

If questions about home monitoring arise, the family of an infant who experienced BRUE should be informed that a home apnea monitor has not been shown to prevent SUID and is not indicated for that purpose. Parents and caregivers can be informed that a BRUE is not a risk factor for SUID. In a prospective study, patients who experienced what was then termed ALTE did not experience SUID. The Collaborative Home Infant Monitoring Evaluation study instituted home monitoring for more than 1,000 healthy term infants and found that 43% of term infants experienced apnea or bradycardia episodes, which indicates that these cardiorespiratory events are common in all infants and are unlikely to be precursors to SUID. Furthermore, SUID usually occurs during infant sleep, whereas an estimated 50% of BRUEs occur during wakefulness.

High-Risk Brief Resolved Unexplained Event

If the patient does not meet all the criteria for low-risk BRUE, the patient is considered high risk. For these infants, if any localizing signs or symptoms exist, the workup should be directed toward that diagnosis. The infant who was not fully resuscitated in the field should be resuscitated, stabilized, and admitted. Any identifiable conditions, such as sepsis, seizures, and gastroesophageal reflux, should be appropriately managed.

Prognosis

Further research is necessary to determine the prognosis for the child who has experienced a BRUE. Parents and caregivers can be assured that most BRUEs are isolated events and the risk of a chronic condition (eg, seizure disorder) is extremely rare.

CASE RESOLUTION

The infant succumbed to SUID. Despite resuscitative efforts by the paramedics, he could not be revived. The mother was advised of the diagnosis of suspected SUID and referred to appropriate agencies and support groups. The coroner was notified of the case. The mother was advised that a coroner investigator would visit her to learn more about the circumstances surrounding the sudden death of her infant.

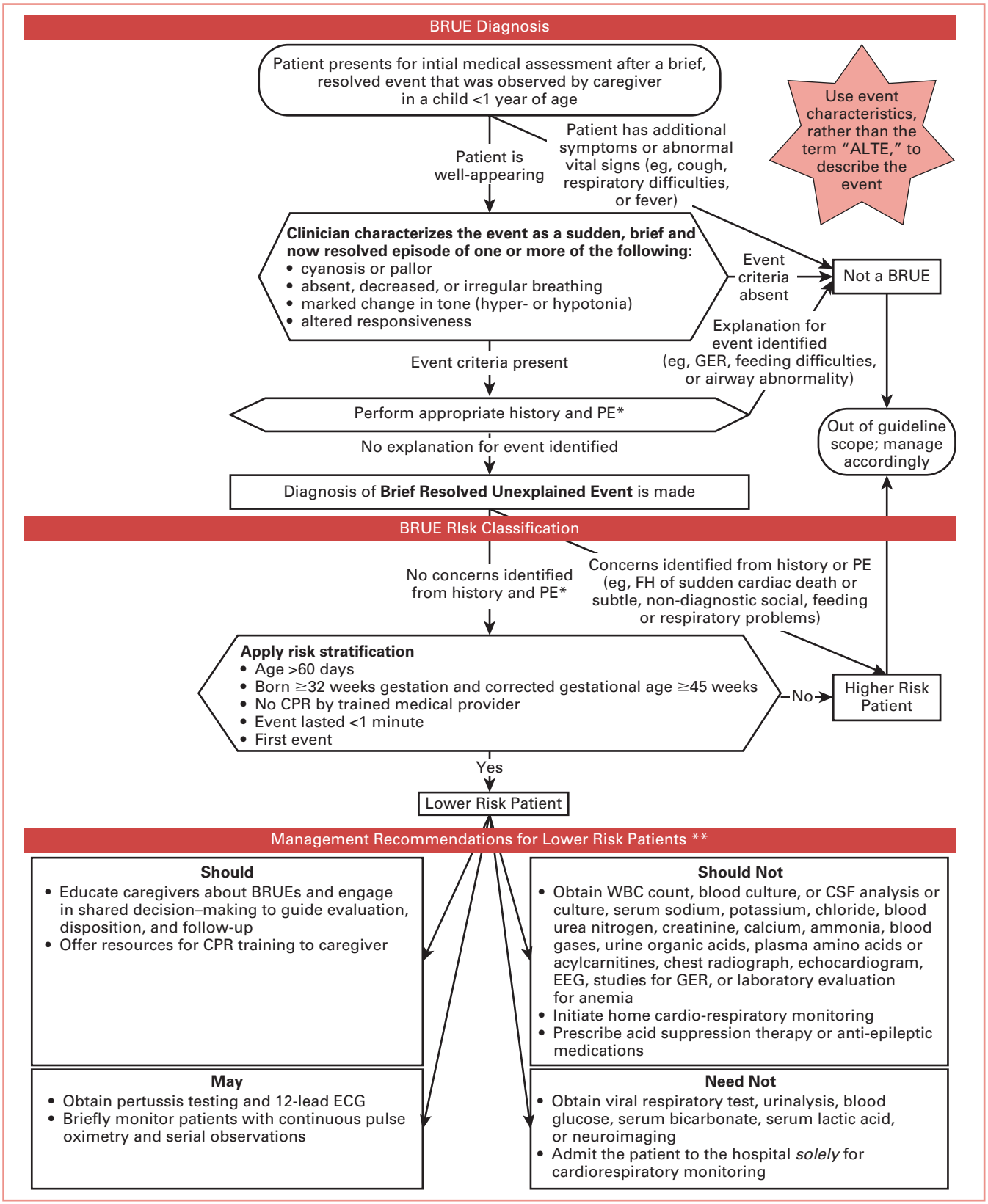

Figure 72.1. Diagnosis, risk classification, and recommended management of a BRUE.

Abbreviations: ALTE, apparent life-threatening event; BRUE, brief resolved unexplained event; CPR, cardiopulmonary resuscitation; CSF, cerebrospinal fluid; ECG, electrocardiography; EEG, electroencephalogram; FH, family history; GER, gastroesophageal reflux; PE, physical examination; WBC, white blood cell.

* Refer to Tables 3 and 4 in www.pediatrics.org/cgi/doi/10.1542/peds.2016-0591 for the determination of an appropriate and negative history and PE.

** Refer to Figure 2 in www.pediatrics.org/cgi/doi/10.1542/peds.2016-0591 for the American Academy of Pediatrics method for rating of evidence and recommendations.

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CHAPTER 73

Syncope

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CASE STUDY

A 16-year-old girl presents to your office with the chief report of fainting at marching band practice on the day prior. She has been in marching band for the past 2 years and states that nothing like this has occurred before. She is concerned about fainting again. She tells you that she "wasn't able to eat or drink" on the day she fainted because she was too busy studying for finals.

She reports that practice was fairly routine up until her fainting episode. Prior to the episode, she was standing in the field, listening to her teacher give instructions for a new routine. The last thing she remembers after standing awhile was feeling lightheaded and sweaty. The next thing she can recall is lying on the ground with her classmates and teacher around her. She denies any chest pain, shortness of breath, or palpitations prior to the episode. Her teacher told her she was unconscious for approximately 10 to 15 seconds without any shaking of extremities. She was immediately back to baseline after she woke up. She denies incontinence. She says that when she stands up too quickly she sometimes feels lightheaded for a few seconds, but she had never fainted before yesterday.

When asked, she denies any past significant medical history. Her mother states that she is very healthy. She has only gone to the emergency department 1 time previously, when she was 2 years old. At that time, she passed out for 30 seconds after crying. She was diagnosed with a breath-holding spell and has not had any other issues since. There is no family history of sudden death and seizures. When questioned alone, she denies use of any illicit drugs or any sexual activity. Her mother asks if it is okay for her to continue to participate in physical activities. She has recently read about sudden death in high school athletes.

The girl's physical examination is unremarkable, and all vital signs are within normal limits for age. Electrocardiography shows normal sinus rhythm with normal voltages and intervals for her age.

Questions

1. What are the causes of syncope?
2. What workup is recommended to evaluate for syncope?
3. When should patients who experience syncope be referred to a subspecialist?
4. Which pediatric subspecialists assist in the evaluation of a patient with syncope?
5. Which patients presenting with syncope are at greatest risk for sudden death?

Syncope, or fainting, is a transient loss of consciousness and tone; it is a common clinical problem in pediatric patients, particularly during puberty and adolescence. The most common causes of syncope in pediatric patients are benign neurocardiogenic events; however, in rare instances syncope is a harbinger of sudden death from arrhythmia, obstruction of aortic outflow, or other serious cardiovascular events.

The 3 general categories of syncope are neurocardiogenic (also called vasovagal syncope), cardiac syncope, and noncardiac syncope (Box 73.1). The workup for syncope can easily become expensive and time-consuming, and it may provide little information beyond that gleaned by the initial history and physical examination. It is the role of the pediatrician to appropriately direct the evaluation for syncope so that a cost-effective evaluation may occur without missing the patient who may be at risk for a sudden death event.

Epidemiology

Syncope is a temporary, transient loss of consciousness and muscle tone that usually is associated with rapid recovery. It is the result of decreased cerebral blood flow that can occur through many different mechanisms. Syncopal events are very common in the pediatric population; up to 50% of college undergraduates have reported experiencing syncope or near syncope, and it accounts for approximately 1% of all pediatric emergency department visits. Females are more commonly affected than males, and the mean age at presentation is 10 to 12 years. Syncope is uncommon in children younger than 5 years. Many cases of syncope quickly resolve and medical attention is not sought; thus, the true incidence of syncope is almost certainly underestimated.

Clinical Presentation

The clinical presentation of syncope varies with the etiology. Vasovagal syncope often is associated with a prodrome of symptoms, including lightheadedness, visual disturbances, nausea, and diaphoresis. The patient has usually been standing for a long period or has suddenly moved from the supine or sitting position to standing. Other forms of neurally mediated syncope include hair-grooming syncope, which occurs mostly in girls while combing, brushing, or blow-drying their hair. Micturition syncope, although

Box 73.1. Causes of Syncope

Neurocardiogenic (ie, Vasovagal Syncope)

Cardiac

- Tachyarrhythmias
  - Supraventricular tachycardia
  - Ventricular tachycardia
- Bradyarrhythmias
  - Second- or third-degree heart block
  - Sinus node dysfunction
- Left or right ventricular outflow tract obstruction
  - Hypertrophic cardiomyopathy
  - Aortic stenosis
- Idiopathic pulmonary hypertension
- Coronary artery disease
  - Acquired coronary artery disease
    - Kawasaki disease
  - Congenital coronary anomaly
    - Intramural coronary artery
    - Anomalous origin of a coronary artery
- Primary cardiac dysfunction
  - Dilated cardiomyopathy
  - Noncompaction cardiomyopathy
- Secondary cardiac dysfunction
  - Viral or idiopathic myocarditis
  - Restrictive cardiomyopathy

Noncardiac

- Orthostatic hypotension
- Neurologic (eg, seizures, atypical migraine, dysautonomia)
- Breath-holding spells
- Psychogenic (eg, hysteria, hyperventilation)
- Self-induced (eg, hyperventilation, "the choking game")
- Metabolic abnormality (eg, hypoglycemia, anemia)

most common in the elderly, may occur in individuals of any age. Younger patients with this type syncope tend to be male; predisposing factors may include reduced food intake, fatigue, alcohol ingestion, and recent respiratory infection. Micturition syncope often occurs at night when voiding after awakening from sleep (ie, while standing immediately after being recumbent). Recurrences of micturition syncope are rare in young patients. Breath-holding spells in toddlers brought on by anger, pain, fear, or frustration may be associated with syncope; this is an infantile form of cardioinhibitory neurally mediated syncope. Infants who experience syncopal breath-holding spells are more likely to grow up and have neurally mediated syncope (see Chapter 52).

Syncope of cardiac etiology often lacks the prodrome of vasovagal syncope. The main cardiac causes of syncope are arrhythmia and left ventricular outflow obstruction. Patients may report palpitations, chest pain, or chest tightness. Cardiac syncope commonly occurs during physical activity and may be accompanied by complete loss of body tone.

Syncope related to seizures generally has a longer recovery time associated with the postictal phase; witnesses may describe the patient as being dazed or "having a blank look on their face" before fainting. These episodes may occur whether the patient is recumbent or upright.

Pathophysiology

Autonomic

Autonomic causes of syncope are the most common etiology, accounting for up to 80% of cases of syncope that come to medical attention. They are also referred to as neurally mediated reflexive syncope, vasovagal syncope, neurocardiogenic syncope, and, in toddlers, pallid breath-holding spells. They have in common disturbances in autonomic control of heart rate and blood pressure in response to postural changes, bodily functions, pain, fear, or other strong emotional events. Vasovagal syncopal events usually occur when the patient is upright, resulting in decreased venous return, decreased arterial blood pressure, and decreased left ventricular volume. The resultant reflex stimulation of vagal fibers results in bradycardia, vasodilation, and worsening hypotension (ie, Bezold-Jarisch reflex). The 3 clinical types of neurally mediated syncope are vasodepressor, which starts and is primarily marked by profound hypotension; cardioinhibitory, which is marked by severe bradycardia or even brief asystole; and mixed response, which is a mixture of both vasodepressor and cardioinhibitory types.

Cardiac

Cardiac causes of syncope are more likely than noncardiac causes to be associated with sudden death than non-cardiac causes, so it is important to identify and treat these abnormalities. Cardiac mechanisms of syncope are mainly related to obstructive lesions or arrhythmias. Obstructive lesions cause decreased ventricular outflow, resulting in decreased cerebral perfusion; arrhythmia may result in decreased ejection volume, also causing cerebral hypoperfusion and syncope.

Left-sided obstructive lesions, including aortic stenosis and hypertrophic cardiomyopathy, are the most likely cause of obstructive syncope. Rarely, syncope is caused by pulmonary stenosis or severe primary pulmonary hypertension, mitral stenosis, atrial myxoma, or cardiac tamponade. Cardiac syncope, unlike routine vasovagal syncope, often occurs during exertion, because of the inability of the heart to increase cardiac output to meet the demands placed on it by increased physical activity. Increased diastolic pressure caused by an obstructive lesion may also decrease myocardial perfusion, resulting in cardiac ischemia, dyskinesis, or ventricular arrhythmias, thereby further decreasing ventricular output.

Anomalous origin of the coronary arteries is not an obstructive lesion; however, it too may cause syncope with exercise. The left coronary artery may arise from the pulmonary artery, delivering deoxygenated blood to the left coronary system; alternatively, the left coronary artery may arise from the right coronary cusp and course between the aorta and pulmonary arteries. When the patient is in a high cardiac output state, such as during exercise, the left coronary artery may be compressed between the great arteries, resulting in ischemia or arrhythmia.

Primary arrhythmias causing syncope are a rare but important cause of syncope. Typically, chest radiography, echocardiography, and other imaging modalities are normal, with no evidence of structural heart disease or pulmonary edema. Supraventricular tachycardia may cause syncope or near syncope. In most pediatric patients, the tachycardia is propagated through a concealed pathway, and the resting electrocardiogram (ECG) is normal if the tachycardia is not occurring while the ECG is being obtained. Supraventricular tachycardia may also be associated with Wolff-Parkinson-White syndrome, which itself is characterized by a short P-R interval followed by an abnormally wide QRS complex with an initial delta wave.

Ventricular tachycardia is rare in children with no underlying structural heart disease, but it may be brought on by infection (especially myocarditis or pericarditis), cardiomyopathies, drugs (eg, cocaine, amphetamines), drug interactions (eg, non-sedating antihistamines taken with erythromycin or ketoconazole), and long QT syndrome.

Patients with long QT syndrome have prolonged cardiac repolarization, which usually manifests on the resting ECG as a prolongation of the corrected QT interval. The prolongation of the repolarization period of the heart puts patients with long QT syndrome at risk for torsades de pointes, a malignant form of ventricular tachycardia. The genetic forms of long QT syndrome result from mutations in genes that code for ion transport channels or related proteins. Jervell and Lange-Nielsen syndrome is an autosomal-recessive form of long QT syndrome that is associated with congenital deafness. Autosomal-dominant long QT syndrome that is not associated with congenital deafness has been referred to as Romano-Ward syndrome. Although the clinical diagnosis of long QT syndrome is based on a QTc that is prolonged for the patient's age, an estimated 20% of patients with a gene mutation associated with long QT syndrome have a normal resting ECG; thus, a critical part of the evaluation of the syncopal patient is obtaining a family history of long QT syndrome, sudden death or near sudden death, seizures, or a history of torsade de pointes. Long QT syndrome also may be brought on by electrolyte imbalance, increased intracranial pressure, or medications (Table 73.1).

Table 73.1. Drugs Known to Increase the Risk for Ventricular Arrhythmia in Patients With Long QT Syndrome[a]

Drug	*Class*	*Clinical Use*
Amiodarone hydrochloride	Antiarrhythmic	Abnormal heart rhythm
Arsenic trioxide	Anticancer	Leukemia
Bepridil hydrochloride	Antianginal	Heart pain
Chloroquine	Antimalarial	Malaria infection
Chlorpromazine	Antipsychotic/antiemetic	Schizophrenia/nausea
Cisapride	GI stimulant	Heartburn
Clarithromycin	Antibiotic	Bacterial infection
Disopyramide	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Sedative/antiemetic	Anesthesia adjunct/nausea
Erythromycin	Antibiotic/GI stimulant	Bacterial infection/Increase GI motility
Halofantrine hydrochloride	Antimalarial	Malaria infection
Haloperidol	Antipsychotic	Schizophrenia, agitation
Ibutilide fumarate	Antiarrhythmic	Abnormal heart rhythm
Levomethadyl acetate	Opiate agonist	Pain control, narcotic dependence
Mesoridazine	Antipsychotic	Schizophrenia
Methadone hydrochloride	Opiate agonist	Pain control, narcotic dependence
Pentamidine isethionate	Anti-infective	Pneumocystis pneumonia
Pimozide	Antipsychotic	Tourette syndrome tics
Procainamide hydrochloride	Antiarrhythmic	Abnormal heart rhythm
Quinidine	Antiarrhythmic	Abnormal heart rhythm
Sotalol hydrochloride	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin	Antibiotic	Bacterial infection
Thioridazine	Antipsychotic	Schizophrenia

Abbreviation: GI, gastrointestinal.

[a] For a complete list of drugs to avoid in patients with long QT syndrome, visit www.crediblemeds.org.

Noncardiac

Noncardiac causes of syncope include neurologic etiologies (eg, seizures, migraines), metabolic disturbances (eg, hypoglycemia), hyperventilation (panic attacks or self-induced), and hysteria. Low iron stores have been associated with neurally mediated syncope in both children and adolescents and may provide a partial explanation for the higher incidence of neurocardiogenic syncopal events in adolescent girls than boys. Seizures may be difficult to distinguish from vasovagal events, because both can have tonic-clonic movements. Unlike vasovagal or cardiac syncope, seizures result in unconsciousness secondary to neurologic dysfunction. Syncope associated with hypoglycemia is caused by the insufficient delivery of substrate (glucose) to the brain. Cerebral vasoconstriction secondary to arterial hypocapnia produces syncope with hyperventilation that may be secondary to panic attacks or may be self-induced. The "choking game" or "fainting game" refers to intentional cutting off of oxygen to the brain, with the goal of inducing a "high" or euphoric feeling, usually resulting in syncope and occasionally in serious injury or death. Hysterical syncope lacks a true prodrome, and patients usually suffer no injury when they fall. This form of syncope is thought to be related to Munchausen syndrome.

Differential Diagnosis

The differential diagnosis of syncope is presented in Box 73.1. Events that precede and follow the syncopal event are key in determining the etiology of syncope.

Evaluation

History

A thorough history should be obtained from the family and patient, focusing on the patient's symptoms, the situation surrounding the event, and the family history (Box 73.2). A primary goal of the history is to identify any underlying cardiac problems, because these patients are at the greatest risk for sudden death.

Physical Examination

The patient with syncope must undergo a thorough physical examination. Physicians should assess the blood pressure to screen for hypotension and hypovolemia. The cardiac examination should include palpation of the chest for the point of maximal intensity, thrills and lifts, and auscultation to assess the intensity of the heart sounds and detect the presence of murmurs or other adventitial sounds. Upper- and lower-extremity pulses should be palpated for their presence and quality. The remainder of the examination should focus on identifying any abnormal neurologic findings.

Laboratory Tests

The history and physical examination should guide which laboratory tests are necessary. Generally, few tests are needed. Serum glucose level shortly after the syncopal event may be abnormally low and reveal hypoglycemia. Fasting glucose or glucose tolerance tests are usually normal, and such testing is not indicated. In pubertal females, a pregnancy test should be obtained as well as a hemoglobin level. Iron levels may be low in patients with neurally mediated syncope.

Box 73.2. What to Ask

Syncope

- What was the patient doing when the episode occurred?
- What was the position of the patient?
- Did the patient have any symptoms before the syncopal event?
- Did the patient have any chest pain or palpitations during the event?
- How long did it take for the patient to recover from the syncopal event?
- Were any residual symptoms present after the syncopal event?
- Has the patient recently been ill, dehydrated, or fatigued?
- Does the patient have a history of underlying cardiac disease?
- Is the patient taking any type of medication (prescribed, over-the-counter, or illicit)?
- Does the patient have a history of breath-holding or pallid spells?
- Is there a family history of sudden death, seizures, deafness, or cardiac abnormalities?

Imaging Studies

Every patient who is being evaluated for syncope requires an ECG. The ECG may reveal Wolff-Parkinson-White syndrome or a prolonged QT interval, neither of which can be diagnosed on history and physical examination alone. These studies also can be useful in identifying underlying structural abnormalities, such as right ventricular hypertrophy secondary to pulmonary hypertension, left ventricular hypertrophy secondary to hypertrophied cardiomyopathy, or Q waves associated with anomalous origin of the coronary arteries. Patients with findings suggestive of cardiac disease, that is, with a positive history, physical findings, or an abnormal ECG, require referral to a pediatric cardiologist for further evaluation. The cardiac workup of syncope may include a Holter monitor or an event recorder. The Holter monitor is worn for 24 hours and continuously records the heart rhythm. Because this is a limited window of observation, the Holter monitor captures arrhythmia less than 20% of the time, even in patients with known arrhythmias. Event recorders are worn for longer periods, often up to several weeks. They can record and retain the cardiac rhythm before, during, and after an event. When the patient activates the monitor, the recording is saved for download to the cardiologist. If the monitor is not activated, the event recorder will not save the information but will record over it. Although the event recorder has a higher probability than a Holter monitor of capturing an arrhythmia, the tracings are generally lower quality. Small, digital ambulatory cardiac monitors are a relatively new innovation. They are waterproof, may be worn for up to 14 days, and may provide benefits of both the Holter monitor and the traditional event recorder. Exercise stress testing is often used to evaluate the patient's response to exertion and potentially replicate symptoms in a monitored setting. Electrophysiology studies may be ordered if an arrhythmia is uncovered during the evaluation.

The workup for patients without evidence of cardiac disease, that is, with a negative family history for cardiac disease or sudden death and no exertional symptoms such as chest pain, should focus on the noncardiac or autonomic causes of syncope. Patients with prolonged recovery time or persistent neurologic symptoms following an event should be referred to a neurologist and may require electroencephalography to rule out seizure disorders.

A tilt test may be used to aid in the diagnosis of vasovagal syncope, although in most cases the history is sufficient. For this test, the patient is placed on a table that is then tilted to simulate standing in an upright position, a condition that is commonly associated with vasovagal syncope. Great variability exists in the tilt test, however, with a false-positive rate of up to 20%. Factors that influence the test results include the time of day, whether the patient has fasted, hydration status, and whether the test was augmented with isoproterenol. Few false-negative tilt test results have been reported; however, because of the high number of false-positive results the tilt test should be reserved for refractory, recurrent, or unexplained syncope only.

Management

Management of syncope depends on its cause. Recurrent vasovagal syncope may be treated simply with increased fluid intake, including carrying a water bottle in school, and increased salt intake. For patients who are not responding to conservative measures and who are experiencing recurrent vasovagal syncope, it is reasonable to prescribe midodrine hydrochloride. Fludrocortisone acetate, a mineralocorticoid, is a common medical intervention for vasovagal syncope, although the efficacy is not well established. Other treatments include vagolytic drugs (eg, disopyramide), or centrally acting drugs (eg, imipramine, fluoxetine). These medications have varied benefits, and results between small controlled trials are not consistent. The use of beta blockers is not beneficial and may result in a higher recurrence rate.

Patients with neurologic syncope secondary to seizures should be treated with anticonvulsants. Patients with hyperventilation, hysteria, or hypoglycemia are most amenable to behavioral interventions. Patients with syncope secondary to a cardiac etiology should be referred to a cardiologist for further evaluation and correction of the underlying problem. Syncopal episodes of a cardiac etiology may require more aggressive management, such as surgery or cardiac pacing, because they are more likely to result in sudden death.

Prognosis

The prognosis for autonomic and noncardiac syncope is good. Often, patients with vasovagal syncope experience only a single event, and those with recurrent events can be treated with increased fluid intake or with medication. One subgroup to be aware of is children with pallid breath-holding spells; although these spells resolve by 5 years of age in most children, up to 17% of patients may continue to have syncope in adulthood. Patients who have syncope with an underlying cardiac etiology are at the greatest risk for sudden death, and it is only through identification and treatment of these structural or rhythm abnormalities that sudden death may be prevented.

CASE RESOLUTION

The adolescent girl describes symptoms consistent with vasovagal syncope. Her family history, physical examination, and ECG are not suggestive of underlying cardiac disease. The patient and her family should be informed that certain factors, such as dehydration, fatigue, and hunger, can precipitate syncope. Behavioral changes, such as eating breakfast and drinking plenty of water, should be implemented to prevent or limit recurrence of syncope. The patient should be encouraged to carry a water bottle in school, and if necessary a physician note should be sent to the school to allow her to do so. Management with medications is not indicated at this time.

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CHAPTER 74

Shock

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CASE STUDY

A 7-month-old boy is brought in by his parents with a history of vomiting and diarrhea for 2 days. He also has had a low-grade fever and, according to his parents, has become progressively more listless. Vital signs show a heart rate of 200 beats per minute, respiratory rate of 30 breaths per minute, and blood pressure of 72/35 mm Hg. The infant is lethargic, and his skin is mottled. Capillary refill time is 3 seconds. His anterior fontanelle is sunken, and his mucous membranes are dry. The abdomen is flat and nontender, and hyperactive bowel sounds are heard.

Questions

1. What is shock, and what clinical signs can help in the recognition and assessment of shock?
2. What are the stages of shock?
3. What are the different types of shock, and what are the possible causes of each type?
4. What are the management priorities in treating shock?

Shock is defined as a state of circulatory dysfunction resulting in insufficient delivery of oxygen and other metabolic substrates to the tissues. Shock is not a disease but rather an abnormal physiologic state that may result from many disease processes. Early recognition and prompt management of shock are critical to avoid permanent end-organ damage or death.

Epidemiology

The most common type of shock in children worldwide is hypovolemic shock, and the most common causes are dehydration resulting from gastrointestinal infections that cause vomiting and diarrhea, and hemorrhage resulting from traumatic injury. Epidemiology may differ in tertiary care health care systems in developed countries, however. In a case series of 147 pediatric patients with shock (excluding trauma patients) from Children's Hospital of Nevada at UMC, septic shock was the most common etiology, with 57% of patients presenting with that type. Of the remaining patients, 24% had hypovolemic shock, 14% had distributive shock, and 5% had cardiogenic shock. Shock may occur in any age group, but it is more difficult to recognize the early stages in young children because early clinical signs of shock in children are subjective and may be attributed to other causes. By the time young children have developed more typical signs, such as a thready pulse and hypotension, they are in the late stages of shock.

Clinical Presentation

Early signs of shock include tachycardia; cool, clammy, pale, or mottled skin; and delayed capillary refill time. The patient may have a history of decreased urine output. In this early compensated stage, perfusion to vital organs, such as the brain and heart, is maintained by compensatory physiologic processes. As the shock state progresses it becomes uncompensated, resulting in impairment of vital organ perfusion. Signs of uncompensated shock include hypotension; altered mental status (eg, irritability, lethargy, decreased interactivity); weak, thready, or absent pulses (although pulses may be bounding in "warm" septic shock); and severely mottled or cyanotic skin (Box 74.1). In the Nevada epidemiologic study, young children commonly presented with poor extremity

Box 74.1. Diagnosis of the Stages of Shock

Compensated

- Tachycardia
- Normal blood pressure
- Normal or bounding pulses
- Normal or cool, clammy skin
- Pale or mottled skin color
- Alert, anxious mental state
- Mildly delayed capillary refill time
- Decreased urine output

Uncompensated

- Tachycardia or bradycardia
- Hypotension
- Weak, thready, or absent pulses
- Cool, clammy skin
- Severely mottled or cyanotic skin color
- Altered mental state, lethargic
- Delayed capillary refill time
- Decreased or absent urine output

Irreversible

- Multiple organ failure and death

perfusion and poor pulses, whereas adolescents presented with hypotension. Irreversible shock occurs when multiple organs fail and death occurs.

Pathophysiology

Shock occurs when oxygen delivery to tissues is impaired. Adequate oxygen delivery depends on sufficient blood oxygen content and adequate circulatory blood flow (Figure 74.1). The oxygen content in blood depends primarily on the concentration of hemoglobin and the amount of oxygen bound to hemoglobin. In children, oxygen consumption by end organs depends most on oxygen delivery, whereas in adults it depends on oxygen extraction by the tissues.

Blood flow, or cardiac output, is determined by heart rate and stroke volume. Stroke volume depends on preload, contractility, and afterload. *Preload* refers to the amount of blood entering the heart from the systemic vasculature. Increasing preload, for example, via administration of intravenous (IV) fluid boluses, will increase cardiac output until a point of optimal heart muscle fiber length is reached. The Starling curve demonstrates that increased stretching of a muscle fiber results in improved performance of that muscle fiber (ie, improved stroke volume and cardiac output); however, after the point of optimal stretching is reached, performance declines (Figure 74.2).

Contractility, or *inotropy*, is the intrinsic ability of the heart to contract and pump blood to the body. *Afterload* refers to the systemic vascular resistance impeding ejection of blood from the ventricles. Optimal cardiac output depends on sufficient preload, unimpaired cardiac contractility, and the ability of the heart to overcome any afterload. During states of decreased cardiac output resulting in decreased tissue perfusion, adults compensate primarily by decreasing systemic vascular resistance, increasing cardiac contractility, and increasing heart rate, whereas children compensate primarily by increasing their heart rate and by vasoconstriction (to preferentially redistribute blood to essential organs, such as the heart and brain). The vasoconstriction in children may make hypotension a late sign of shock. Irreversible septic shock in adults is often caused by vasomotor collapse, whereas in children cardiac failure plays a larger role in this type of shock.

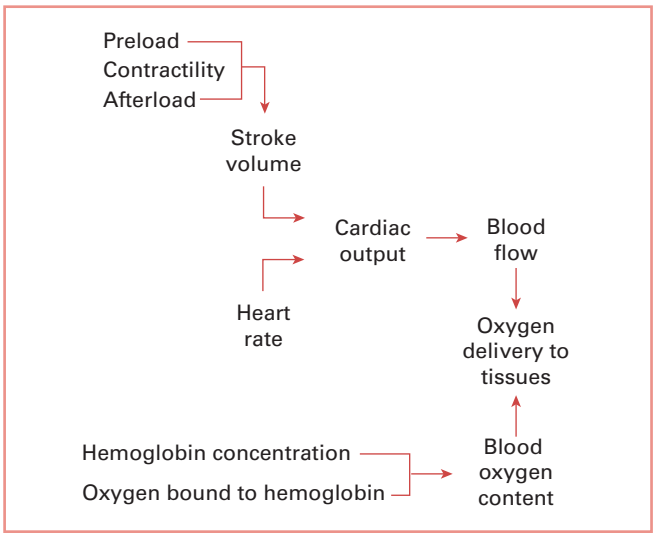

Figure 74.1. Pathophysiology of shock. Factors affecting oxygen delivery to tissue.

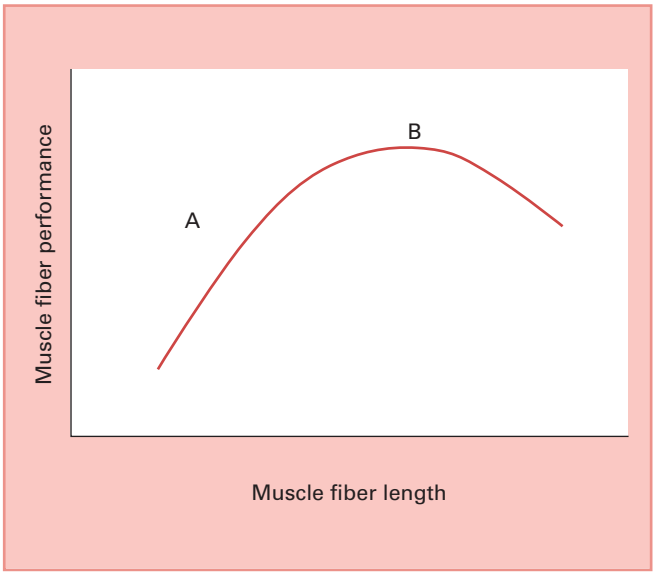

Figure 74.2. Starling curve of cardiac output. As muscle fiber length increases (A), performance increases. After muscle fiber reaches its optimal length (B), performance declines.

Differential Diagnosis

The several types of shock differ based on the underlying pathophysiology (Table 74.1). Hypovolemic shock is the most common type occurring in children and usually results from dehydration or traumatic hemorrhage. Hypovolemia results in inadequate preload, which leads to impaired cardiac output and impaired perfusion. Other causes of hypovolemic shock include dehydration caused by osmotic diuresis in diabetic ketoacidosis and third spacing of fluids (ie, shifting from intravascular to extravascular sites) from peritonitis and burns. Nontraumatic hemorrhage may occur from entities such as epistaxis, gastrointestinal bleeding, and vessel fistula formation.

Distributive shock is a relative hypovolemia; vasodilation results in inadequate circulating blood volume relative to the vasodilation (ie, the "tank" has been made larger by vasodilation, resulting in insufficient fluid to fill the tank). Causes include anaphylaxis and sepsis, which result in the release of vasoactive mediators that cause vasodilation. Spinal cord injury, which can result in neurogenic shock, may result in loss of sympathetic nerve-mediated vascular tone and subsequent vasodilation. Certain ingestions, such as iron, barbiturates, and tricyclic antidepressants, can cause vasodilation and distributive shock.

Cardiogenic shock is an uncommon but important cause of shock in children. Congestive heart failure caused by a congenital heart lesion, myocarditis, or cardiomyopathy results in impaired cardiac contractility and decreased cardiac output. Tachydysrhythmias, such

Table 74.1. Types of Shock

Type of Shock	*Physiologic Mechanism*	*Common Causes*
Hypovolemic	Inadequate preload	Dehydration Traumatic hemorrhage Nontraumatic hemorrhage Diabetic ketoacidosis Peritonitis Burns
Distributive	Relative hypovolemia resulting from vasodilation	Sepsis Anaphylaxis Neurogenic Toxin-mediated
Cardiogenic	Decreased contractility	Congestive heart failure from congenital lesions Myocarditis Tachydysrhythmias
Obstructive	Impaired cardiac output to systemic circulation	Pulmonary embolus Pericardial tamponade Tension pneumothorax Ductal-dependent cardiac lesions
Dissociative	Abnormal hemoglobin—inadequate oxygen bound	Carbon monoxide poisoning Methemoglobinemia

as supraventricular tachycardia, may also result in cardiogenic shock because they do not allow sufficient time for the ventricles to fill with blood, resulting in decreased stroke volume.

Rare causes of shock in pediatric patients include obstructive and dissociative types. In *obstructive shock*, cardiac output to the systemic circulation is obstructed as the result of pulmonary embolus, cardiac tamponade, or tension pneumothorax. Closure of the ductus arteriosus in a neonate with a ductal-dependent congenital heart lesion is another cause of insufficient cardiac output and obstructive shock. In *dissociative shock*, abnormal hemoglobin (eg, methemoglobin), or carboxyhemoglobin caused by carbon monoxide poisoning results in decreased oxygen bound to hemoglobin and decreased oxygen delivered to tissues.

Septic shock combines elements of distributive, hypovolemic, and cardiogenic shock. Vasoactive mediators cause decreased systemic vascular resistance and relative hypovolemia. Third spacing of fluid results in a true intravascular hypovolemia as well. Additionally, mediators of sepsis cause impaired cardiac function.

Because shock is a physiologic state resulting from a variety of etiologies and because it is recognized through clinical findings, it is important to interpret individual findings in the context of the patient as a whole. Heart rate may be elevated for many reasons, including fear, anxiety, and fever. Capillary refill may appear delayed in the extremities of a child who is cold. Blood pressure may appear artificially low when too large a cuff is used to measure it. The health professional must consider whether the child's history is consistent with risk for shock and whether the physical examination as a whole supports the diagnosis.

Evaluation

Early recognition and prompt treatment of shock is the goal. A rapid, focused history and physical examination should be performed to identify patients in shock, and early therapy should be instituted before taking the time to perform a more complete evaluation. Recognition of shock depends on history and physical examination alone; therapy should never be withheld while awaiting results of diagnostic tests.

History

A history of vomiting with or without diarrhea, decreased oral intake, and decreased urine output, especially in infants, should alert the physician to possible hypovolemic shock. Children presenting with major trauma should be evaluated for hemorrhagic shock. A history of fever, lethargy, or irritability, and sometimes a rash, may point toward septic shock. Patients with asplenia, sickle cell disease, or indwelling catheters and those who are immunocompromised (eg, young infants or children on chemotherapy) are at increased risk for sepsis. Children in cardiogenic shock may have a history of a murmur, poor feeding, sweating with feeds, cyanosis, tachypnea, or dyspnea, and the older child may have a history of palpitations.

Physical Examination

A brief physical examination to identify shock focuses on mental status, vital signs, pulses, and skin signs. Impaired level of consciousness, such as lethargy or lack of recognition of parents, occurs later in shock. Earlier in the process, children are anxious, fussy, or irritable. Tachycardia occurs early in shock but must be interpreted in the context of other signs of shock, because tachycardia also may result from fever, pain, or fear of the examination process. Bradycardia is a late, ominous sign in shock and often results from hypoxemia. Hypotension is also a late sign in pediatric shock. It is important to remember that normal values for heart rate and blood pressure vary by age. The lower limit of acceptable systolic blood pressure in a neonate from birth to 1 month is 60 mm Hg and in an infant from 1 month to 1 year is 70 mm Hg. For a child 1 year or older, the lower limit can be estimated using the formula 70 + (2 × age in years) mm Hg; the lower limit is 90 mm Hg for children 10 years or older. Systolic blood pressures lower than these guidelines represent hypotension and late uncompensated shock. Heart rate and blood pressure values requiring immediate attention are shown in Table 74.2.

Presence and quality of pulses should be checked. Weak, thready, or absent peripheral pulses are indicative of shock. However, in warm septic shock, pulses may be bounding. Skin color, moisture, and temperature give valuable clues to diagnosis. Children in shock may have pale, cyanotic, or mottled skin. Early in shock, however, skin color may be normal. Some infants may also have mottled skin

Table 74.2. Critically Abnormal Heart Rate and Blood Pressure

Age	Bradycardia	Tachycardia	Hypotension
Neonate 0–28 days	<100 bpm	>180 bpm	<60 mm Hg
Infant 1–12 months	<90 bpm	>160 bpm	<70 mm Hg
Child 1–10 years	<60 bpm	>140 bpm	<70 + (2 × age) mm Hg
Child >10 years	<60 bpm	>120 bpm	<90 mm Hg

Abbreviation: bpm, beats per minute.

normally. As with tachycardia, isolated signs must be correlated with the bigger clinical picture to diagnose shock. Decreased perfusion in shock results in cool and clammy skin. This is often best initially appreciated in the hands and feet.

Capillary refill is tested by compressing the capillary bed of a fingertip, palm, or dorsal foot with gentle pressure until it blanches. On release, color should return in 2 seconds or less; a capillary refill time of 3 seconds or more is abnormal and indicative of shock. Children in warm septic shock may display "flash" (ie, shortened) capillary refill time. Capillary refill should be tested with the extremity elevated above the heart so that arterial, not venous, perfusion is tested. Additionally, cool ambient temperatures can falsely delay capillary refill times.

In hypovolemic shock caused by dehydration, the patient should be assessed for signs of dehydration, such as dry mucous membranes, lack of tears, sunken eyes, sunken anterior fontanelle in infants, and poor skin turgor. Often, the degree of dehydration can be estimated clinically (see Chapter 80). Patients with hemorrhage, whether traumatic or nontraumatic, must be examined thoroughly to locate the source of hemorrhage.

Children with congestive heart failure and cardiogenic shock may demonstrate dyspnea on exertion, tachypnea, orthopnea, rales, hepatomegaly, gallop rhythm, and a heart murmur; these physical examination signs may be difficult to appreciate in a tachycardic, fussy, ill child. Jugular venous distention and peripheral edema are appreciated less often in children compared with adults. Other signs may include hepatomegaly and/or cardiomegaly on chest radiography as well as a differential in pulses, blood pressure, or pulse oximetry between upper and lower extremities.

Ductal-dependent cardiogenic shock should be suspected in the newborn who presents with shock and/or severe cyanosis unresponsive to oxygen therapy in the first few weeks after birth. Cardiac tamponade is suspected in the patient with muffled or decreased heart tones, paradoxical pulse (ie, decrease in systolic blood pressure >10 mm Hg during inspiration), and distended neck veins. Tension pneumothorax is suspected in patients with deviated trachea (ie, away from the affected side), decreased breath sounds and hyperresonance to percussion on the affected side, and distended neck veins. Pulmonary embolism is rare in pediatric patients, and the signs are subtle. It is mainly suspected in the presence of predisposing factors.

Approximately 20% of children with septic shock present with the classic adult form of warm shock, including increased cardiac output, hypotension, decreased systemic vascular resistance, warm non-mottled skin, bounding pulses, and flash capillary refill. Because children compensate for shock with vasoconstriction, they are more likely than adults to present with cold septic shock, including decreased cardiac output; increased systemic vascular resistance; normal blood pressure to hypotension; cool, clammy, or mottled skin; thready pulses; and delayed capillary refill. The remaining 20% of children with septic shock present with both decreased cardiac output and decreased systemic vascular resistance. Petechiae or purpura are suggestive of meningococcemia as the etiology of septic shock. A sunburn-like rash may occur in patients with toxic shock syndrome caused by streptococcus or staphylococcus.

Laboratory Tests

The suspected cause of shock dictates which laboratory tests are performed. In hypovolemic shock secondary to dehydration, a chemistry panel should be obtained for electrolyte abnormalities and acidosis. Serial hematocrit determinations and a type and crossmatch are important studies in traumatic and nontraumatic hemorrhage, whether known or suspected. In septic shock, a complete blood cell count and blood cultures should be obtained, as well as cultures of other potential sources of infection (eg, urine, cerebrospinal fluid, wound, indwelling venous access line). Results of coagulation studies, including panels to evaluate for disseminated intravascular coagulopathy, and results of electrolyte studies, including calcium and magnesium levels, are frequently abnormal in sepsis. Hypoglycemia is a common finding in any type of shock, and a rapid bedside glucose determination should be performed for all critically ill pediatric patients. Arterial blood gases can demonstrate adequacy of oxygenation and degree of acidosis and are necessary to diagnose elevated carboxyhemoglobin and methemoglobin levels. Initial lactate levels, particularly in patients with septic shock and in trauma patients, may be correlated with overall prognosis and can be followed serially to chart progress. Procalcitonin is another increasingly popular biomarker followed in suspected sepsis. Troponins may be useful in determining severity of disease and following patients with cardiogenic shock. D-dimer assay is useful in patients with suspected pulmonary embolism.

Other Studies

Chest radiography, electrocardiography, and echocardiography may be obtained for patients with cardiogenic or ductal-dependent obstructive shock to further elucidate the specific etiology. Workup of stabilized trauma patients may include bedside ultrasonography, radiography, or computed tomography. Imaging studies contribute to the diagnoses of cardiac tamponade, tension pneumothorax, and pulmonary embolism. Invasive monitoring with arterial lines for systemic arterial blood pressure and central venous lines for central venous pressure or pulmonary artery wedge pressure may be helpful in the ongoing management of shock, particularly fluid-resistant shock.

Management

The first management priority in the treatment of any critically ill child is attention to airway patency and ventilation. For the patient with significant respiratory compromise, bag-and-mask ventilation followed by endotracheal intubation is performed. Usually, however, patients in compensated shock do not require initial advanced airway management. Instead, the immediate priorities are administration of oxygen and initiation of cardiorespiratory monitoring. Oxygen by mask or nasal cannula, preferably heated and humidified, should be administered immediately. Elective rather than emergent endotracheal intubation should be considered to reduce metabolic demands caused by increased work of breathing. When intubating and sedating patients in shock, sedative agents with fewer hemodynamic effects, such as ketamine or fentanyl, are preferred over those that may contribute to hypotension, such as other opiates, benzodiazepines, and propofol. Etomidate, however, although its effects are hemodynamically neutral, is not recommended in septic shock because of its cortisol suppressive effect. Mechanical ventilation settings should emphasize a lung-protective approach.

Almost concurrently, the next priority is achieving intravascular access and, in most cases, administering fluids. Peripheral IV access should be attempted. If this is unsuccessful after 3 attempts or 90 seconds, an intraosseous line may be placed or IV access may be obtained by placement of a central venous catheter or by cutdown technique. Ultrasound-guided vascular access is another option. Intraosseous lines have been demonstrated to provide much more rapid vascular access compared with central line placement. Umbilical venous lines can sometimes be placed in neonates within the first 1 to 2 weeks after birth. More than 1 intravascular line is usually needed for managing patients in shock.

Decreased preload and hypovolemia (actual or relative) are present in the most common causes of pediatric shock. Cardiogenic shock is the only form of shock that may not benefit from increasing preload via a fluid bolus. For other forms of shock, an initial fluid bolus of 20 mL/kg isotonic crystalloid fluid (maximum 1 L), such as normal saline or lactated Ringer solution, should be rapidly infused over 5 to 10 minutes; this may require manually pushing the fluid using a large syringe or a pressure bag. Fluid boluses can be hand pushed into an intraosseous line. Colloid fluid (eg, albumin) theoretically has the advantage of remaining intravascular a longer period of time than normal saline, but this has not been proved to result in a measurable benefit. Crystalloid fluid is recommended for initial boluses because it is less expensive and more readily available than colloid fluid. If a patient with traumatic hemorrhage remains hemodynamically unstable after 2 crystalloid fluid boluses, packed red blood cells at 10 mL/kg may be required. The patient should be assessed for improvement in mentation, vital signs, peripheral pulses, and skin signs after each fluid bolus. Repeat fluid boluses of 20 mL/kg (1 L) to a total of 80 mL/kg (4 L) or more may be necessary to restore intravascular volume. Patients should be reassessed after each bolus before ordering another bolus. Development of hepatomegaly or rales may indicate fluid overload and the need to begin other therapies, such as vasoactive infusions. This is particularly true for cardiogenic and septic shock.

A well-designed and executed trial performed in Africa, the Fluid Expansion as Supportive Therapy (FEAST) trial, has called into question aggressive fluid resuscitation in patients with septic shock. Although patients randomized to rapid fluid therapy showed earlier improvement in circulatory parameters, their mortality was consistently higher. It has been suggested that the results of this trial may not be generalizable to patients in developed countries because of differences in malaria infection, nutritional status, and other factors. The authors suggest that aggressive fluid therapy is particularly associated with increased mortality in highly acidotic patients, especially in developing countries in which inotropic support and mechanical ventilation may not be available. Currently, expert guidelines still recommend early aggressive fluid therapy for septic shock in developed countries in which inotropes and mechanical ventilation are available.

The mnemonic SHOCKED (sound the alarm, help hypovolemia, optimize oxygenation, constrict and contract, keep in mind underlying causes, electrolytes and glucose normalized, decrease metabolic demand) may be used to recall overall management (Box 74.2). Further management in addition to fluids is dependent on the specific etiology. Patients in septic shock should receive empiric broad-spectrum antibiotic coverage within the first hour after presentation. Patients with toxic shock syndrome should receive antibiotics, including clindamycin. A surgeon must assist in identifying the source of hemorrhage and controlling the bleeding in patients with traumatic hemorrhage and may be required for

Box 74.2. SHOCKED Mnemonic for Management of Shock

- **Sound the alarm:** Obtain help from consultants, intensivists, and ancillary personnel. Move the patient to a monitored room and place on a cardiorespiratory monitor, automated blood pressure measurement, and pulse oximetry.
- **Help hypovolemia:** Get intravascular access and start 20 mL/kg crystalloid fluid bolus. Reassess after each bolus and continue giving boluses unless hepatomegaly or rales develop. Patients may require ≥80 mL/kg of fluids.
- **Optimize oxygenation:** Give supplemental oxygen regardless of pulse oximetry values. Consider elective intubation and artificial ventilation to reduce metabolic demands as indicated. Transfusion may be required if hemoglobin is low (<8–10 g/dL).
- **Constrict and contract:** Use inotropic and vasoconstrictive agents as necessary for fluid-refractory shock.
- **Keep in mind underlying causes:** Give or apply therapies specific to the underlying cause.
- **Electrolytes and glucose normalized:** Measure and normalize electrolytes (especially calcium) and glucose. Control hyperglycemia, with a target of ≤180 mg/dL.
- **Decrease metabolic demand:** Manage hyperthermia and pain to reduce metabolic demand on the patient. Consider elective intubation. Keep patient nil per os (ie, nothing by mouth).

management of nontraumatic hemorrhage as well depending on the specific etiology. Blood transfusions may be required. Spinal cord injury is treated with supportive care in consultation with a neurosurgeon. Anaphylactic shock is treated with IV epinephrine, IV diphenhydramine, antihistamine H_2 receptor blockers, glucocorticoids, and nebulized albuterol. Pericardial tamponade is relieved by pericardiocentesis, tension pneumothorax by needle or tube thoracostomy, and pulmonary embolus with supportive care and thrombolytic agents. Carbon monoxide poisoning is managed with 100% oxygen and, if severe, hyperbaric oxygen therapy. Patients with methemoglobinemia appear cyanotic even while receiving 100% oxygen and may be treated with methylene blue. Supraventricular tachycardia should be managed with adenosine if the patient is hemodynamically stable and with synchronized cardioversion if the patient is unstable. Ductal-dependent obstructive shock should be treated with prostaglandin E_1 (PGE_1) infusion.

Patients with cardiogenic shock require inotropic agents to increase cardiac contractility and improve tissue perfusion. Patients in the later stages of other forms of shock (eg, hypovolemic, distributive, septic) may also suffer cardiac dysfunction. In such patients, only after adequate fluid resuscitation has been performed and signs of shock or hypotension persist (ie, fluid-refractory shock) should inotropic agents be started. Central venous pressure monitoring may be necessary to determine whether fluid resuscitation is adequate. Patients with septic shock may require vasoactive agents to reduce or increase systemic vascular resistance.

Epinephrine or dopamine is often the first-line inotropic agent, with recent literature and expert opinion favoring epinephrine. Guidelines recommend beginning inotropic agents when indicated in a peripheral line until a central line is available; that is, do not delay. At low doses (2–5 mcg/kg/min), dopamine improves renal blood flow and enhances urine output. At midrange doses (5–10 mcg/kg/min), dopamine exerts primarily a β-adrenergic effect, improving contractility and increasing heart rate. At higher doses (10–20 mcg/kg/min), the α-adrenergic effects of dopamine cause peripheral vasoconstriction to improve hypotension. Recent data show increased mortality and increased dysrhythmias in patients receiving dopamine as first-line inotrope; as a result, epinephrine has become the preferred first-line therapy. Epinephrine has predominantly β-adrenergic effects at lower doses (0.05–0.1 mcg/kg/min) and α-adrenergic effects at higher doses (≤1.0 mcg/kg/min). Because epinephrine is a strong inotrope, it is recommended for cold septic shock. Norepinephrine (0.01–1.0 mcg/kg/min) has predominantly α-adrenergic vasoconstrictive effects and therefore is preferred for warm septic shock with low systemic vascular resistance and for distributive shock states (eg, anaphylaxis, neurogenic shock, certain toxin-induced shock states). Dobutamine (1–20 mcg/kg/min) may be the most useful drug for cardiogenic shock because it is selective for β-adrenergic effects, thereby increasing cardiac contractility. In the setting of hypotension, however, dobutamine-mediated peripheral vasodilation may be detrimental. Dobutamine is typically used in a range of 10 to 20 mcg/kg per minute. Combinations of inotropic agents may be beneficial to maximize improvements in cardiac contractility and cardiac output without compromising renal perfusion or worsening hypotension. Dopamine and dobutamine may be less effective in infants younger than 12 months than in older children. This is another reason that some institutions recommend epinephrine as the first-line inotropic agent.

Patients in cardiogenic shock or cold septic shock may also benefit from afterload reduction using systemic vasodilators, such as nitroprusside (0.5–5 mcg/kg/min). If these are used, blood pressure should be continuously monitored, typically in the setting of an intensive care unit. Cold septic shock refractory to epinephrine may also be treated with type 3 phosphodiesterase inhibitors (eg, inamrinone 1–20 mcg/kg/min, milrinone 0.25–1.0 mcg/kg/min), which exert inotropic and vasodilator actions (ie, inodilators). Typically, a pediatric intensive care specialist should be involved in the care of the patient, and central venous pressure monitoring should be begun before vasodilator agents are started.

Neonates with ductal-dependent lesions present with a sudden onset of shock and cyanosis, typically in the first 2 weeks after birth. Common lesions include hypoplastic left heart syndrome, aortic coarctation, and tricuspid atresia. Prostaglandin E_1 (0.1 mcg/kg/min, titrated to effect), which acts to keep the ductus arteriosus open, should be immediately infused if a ductal-dependent lesion is suspected as the cause of shock. Apnea may result from PGE_1 therapy, and attention to airway management is of critical importance.

Historically, it was common to mix vasoactive infusions using the "rule of 6 and 0.6." That is, for dopamine, dobutamine, and nitroprusside, mix 6 mcg/kg of drug with enough dextrose 5% in water to produce a final volume of 100 mL. Infusion at 1 mL per hour provides a dose of 1 mcg/kg per minute. For epinephrine, norepinephrine, and PGE_1, mix 0.6 mcg/kg of drug with enough dextrose 5% in water to produce a final volume of 100 mL. Infusion of 1 mL per hour provides a dose of 0.1 mcg/kg per minute. Calculations such as these are prone to error, however, and computerized order forms with automatic error alerts or "smart" pumps that automatically calculate doses based on the patient's input weight are better choices.

Treatment of patients in shock must include attention to conditions that increase metabolic demand. Acidosis should be assessed, and medical therapy and ventilator management should be done with the intent to improve acid-base status. Temperature should be kept neutral, with antipyretic agents and cooling measures used as needed. Electrolyte abnormalities, particularly hypocalcemia and hypoglycemia, must be assessed and corrected. If a hypothyroid state is suspected, thyroid hormone replacement therapy is important. Blood products may be required for patients with septic shock and disseminated intravascular coagulation. Packed red blood cells, 10 mL/kg at a time, should be administered to maintain hemoglobin of at least 10 g/dL for unstable, hypoxemic, or hemorrhaging patients, and 7 to 9 g/dL for stable patients. Fresh frozen plasma may be administered to correct abnormalities in prothrombin and partial thromboplastin times but should not be pushed because of its propensity to cause further hypotension. Cryoprecipitate should be reserved for documented hypofibrinogenemic states.

An expert panel from the American College of Critical Care Medicine created clinical practice parameters for the treatment of pediatric septic shock (Figure 74.3). Recommended therapy is divided between therapies for the first hour (ie, "golden hour") and therapies beyond the first hour (often with critical care specialists involved). In the first 15 minutes after recognition of septic shock, practitioners should attend to the airway and establish intravascular access, begin fluid boluses in 20 mL/kg increments, and diagnose and correct any hypoglycemia and hypocalcemia. The goal of therapy is normalization of heart rate, blood pressure, and capillary refill (≤2 seconds), no difference between peripheral and central pulses and warm extremities, urine output greater than 1 mL/kg per hour, normal mental status, cardiac index between 3.3 and 6.0 L/min/m^2, and superior vena cava (SVC) oxygen saturation (O_2 sat) 70% or higher. Patients who are responsive to fluid may be observed in the pediatric intensive care unit. Epinephrine infusion should be started for those who remain hypotensive after fluid resuscitation. Norepinephrine infusion is recommended for the less common warm septic shock state. The guidelines emphasize that inotropic therapy should not be withheld because there is no central line; it can be administered peripherally if no other options exist. Two studies of patients transferred into a tertiary pediatric medical center showed significantly reduced mortality and morbidity for patients cared for by community practitioners who followed these guidelines for the first hour of care.

Corticosteroids are controversial in the management of sepsis. Guidelines suggest administering "stress doses" of hydrocortisone 2 mg/kg or 50 mg/m^2 body surface area beyond the first hour of therapy for catecholamine-resistant septic shock in cases of suspected adrenal insufficiency. Adrenal insufficiency may be suspected in patients with a history of a central nervous system abnormality or pituitary abnormality, a known adrenal gland disorder, recent surgery, history of chronic steroid therapy (eg, for asthma, inflammatory bowel disease, a rheumatologic condition), and in purpura fulminans. "Shock doses" of hydrocortisone (50 mg/kg) may be administered in the setting of catecholamine-resistant fulminant septic shock and dopamine-resistant purpura fulminans. It is suggested that a baseline cortisol level be drawn before administering corticosteroids.

After the first hour of therapy, a vasodilator (eg, nitroprusside) or type 3 phosphodiesterase inhibitor (ie, inamrinone, milrinone) along with further volume loading may be helpful in catecholamine-resistant cold septic shock with normal blood pressure and SVC O_2 sat less than 70%. In cases of cold septic shock with low blood pressure and SVC O_2 sat less than 70%, continued titration of epinephrine and volume, addition of norepinephrine, and consideration of other vasoactive drugs is recommended. For warm septic shock, continued titration of norepinephrine and volume is recommended, with the possible addition of vasopressin (0.0003–0.0008 U/kg/min), terlipressin, or angiotensin, and consideration of other vasoactive drugs. Vasopressin and terlipressin have not been well studied in children but show promise in adults. For persistent catecholamine-resistant shock (particularly septic or cardiogenic), consideration may be given to ventricular assist devices or extracorporeal membrane oxygenation. Recombinant activated protein C (ie, drotrecogin alfa) was recommended for some septic adult patients but not for pediatric patients, and the commercial product Xigris is no longer available.

Prevention

Improving outcomes is focused primarily on early recognition and early appropriate therapy of shock. One study showed significantly reduced morbidity and mortality in shock patients transferred to a tertiary pediatric medical center if community hospital physicians recognized shock and used pediatric advanced life support (PALS)–recommended interventions early. Appropriate PALS-recommended therapy was defined as more than 20 mL/kg of fluids (except in those with cardiac conditions) and use of inotropes in patients in fluid-refractory shock. Unfortunately, although 37% of the patients transferred during the study period were in shock, as defined by prolonged capillary refill time or hypotension, only 7% were identified as in shock during the referral process. Early recognition of compensated shock is a key preventive measure to reduce mortality. In the same study, only 36% of those in shock received appropriate PALS-recommended therapy before transfer. Community health professionals must concentrate on obtaining vascular access (with an intraosseous needle, if necessary), giving fluid boluses early, and starting inotropes (through a peripheral IV line, if necessary) for the management of fluid-refractory shock within the first hour. Sepsis recognition bundles including a trigger tool based on vital signs, triage physical examination, and patient risk factors (the trigger tool is often incorporated into electronic medical record systems) with rapid clinician assessment within 15 minutes for those that are trigger positive, are recommended to improve recognition. Early therapy, which often occurs before the patient reaches a tertiary care center, is another important preventive measure. Rapid response teams are increasingly being used in hospitals to institute appropriate medical therapy for inpatients with concerning symptoms or vital signs. At a minimum, community pediatricians should have the ability to administer oxygen and obtain intravascular or intraosseous access and administer rapid fluid boluses in their offices. Early broad-spectrum antibiotic therapy within 60 minutes of recognition of possible sepsis (along with blood culture, but only if it does not delay antibiotic administration) is another important element of recommended resuscitation bundles.

Prognosis

Children in shock are critically ill and at risk for progression to multiorgan failure and death. Prognosis depends on how early shock is recognized and treated and on the underlying etiology. Pediatric septic shock carries a 2% mortality rate in previously healthy children but an 8% mortality rate in children with chronic illness. These rates are significantly improved from 60% in the 1980s and 97% in the 1960s and are also lower than the adult septic shock mortality rate. Mortality rates are even lower with prompt recognition and adequate treatment.

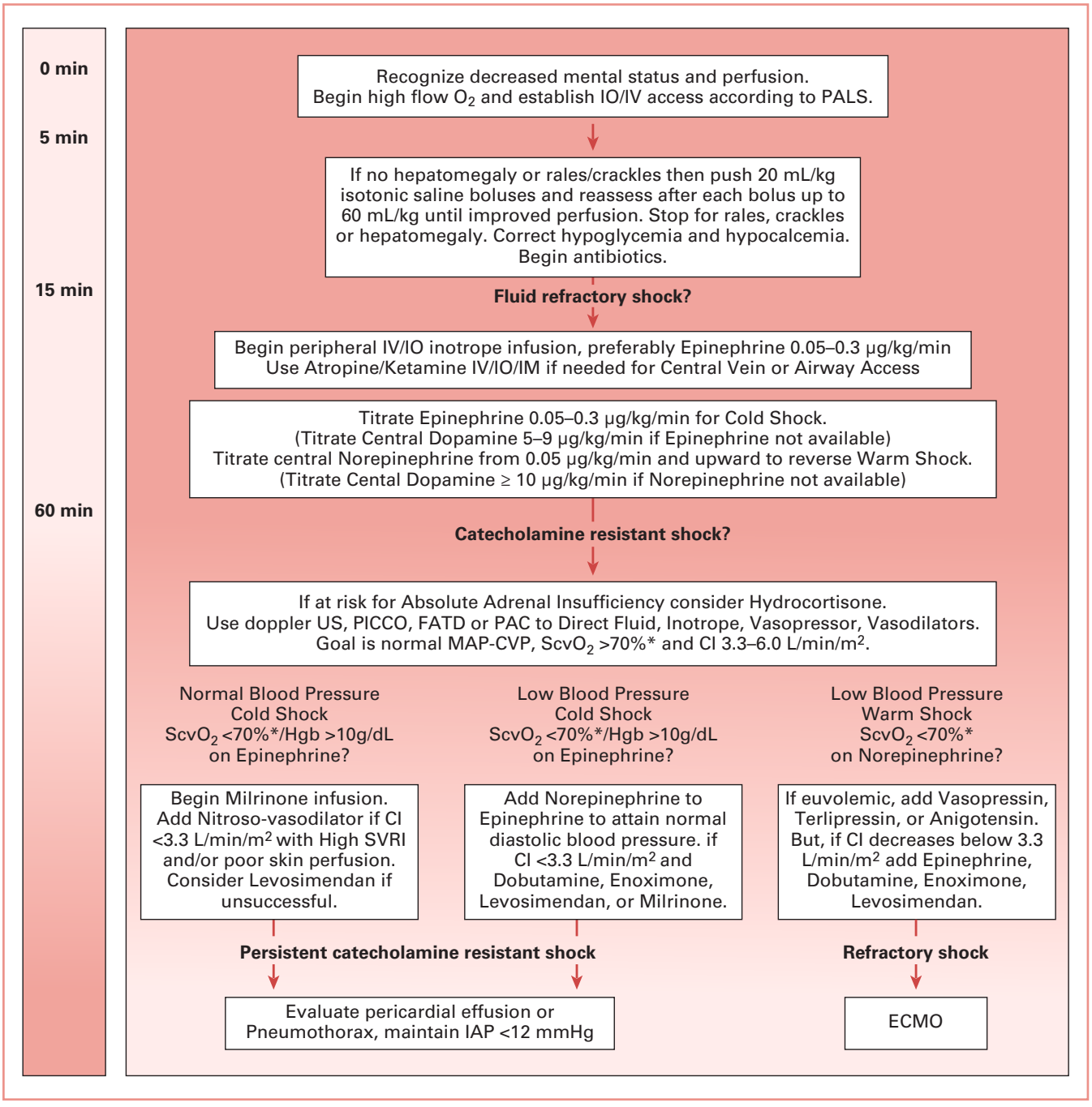

Figure 74.3. American College of Critical Care Medicine algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in infants and children. Proceed to next step if shock persists. 1) First hour goals: Restore and maintain heart rate thresholds, capillary refill within 2 seconds, and normal blood pressure in the first hour/emergency department. 2) Subsequent intensive care unit goals: If shock is not reversed, proceed to restore and maintain normal perfusion pressure (MAP – CVP) for age, $ScvO_2$ > 70% (* except congenital heart patients with mixing lesions), and cardiac index of 3.3 to 6.0 L/min/m^2 in the pediatric intensive care unit.

Abbreviations: CI, cardiac index; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; FATD, femoral arterial thermodilution method; Hgb, hemoglobin; IAP, intra-abdominal pressure; ICU, intensive care unit; IM, intramuscular; IO, intraosseous; IV, intravenous; MAP, mean arterial pressure; PAC, premature atrial contractions; PALS, pediatric advanced life support; PICCO, Pulse index Continuous Cardiac Output; $ScvO_2$, central venous oxygen saturation; SVC, superior vena cava; SVRI, systemic vascular resistance index; US, ultrasonography.

Reprinted with permission from Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. *Crit Care Med.* 2017;45(6):1061–1093.

CASE RESOLUTION

The boy is in barely compensated (ie, not hypotensive) hypovolemic shock resulting from diarrhea, vomiting, and dehydration. He should receive oxygen and cardiorespiratory monitoring, and IV access should be rapidly established. Isotonic fluid boluses of 20 mL/kg should be given, with reassessment performed between each bolus. As much as 80 mL/kg may be needed before improvements in mentation, vital signs, pulses, and skin signs are evident.

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CHAPTER 75

Approach to the Traumatized Child

David B. Burbulys, MD

CASE STUDY

A 6-year-old boy is brought to the emergency department after being struck by an automobile while crossing the street. He was found unconscious at the scene. Initial evaluation shows that he has an altered level of consciousness, shallow respirations, ecchymosis across the upper abdomen, and a deformed, swollen left thigh. The pediatric emergency physician is called in to discuss an initial assessment and management plan for the injured child with the trauma surgeon.

Questions

1. What are the most common mechanisms of injury responsible for trauma in children?
2. What are some of the physiologic differences between adults and children that make children more susceptible to certain types of injury?
3. Which areas of the body are most likely to be injured in a typical automobile versus pedestrian collision?
4. What are the components of a primary survey in pediatric trauma patients?
5. What radiologic and laboratory studies should be performed in children with multiple injuries?

Trauma is often referred to as the neglected disease of modern society. Childhood trauma, in particular, is poorly understood and studied. Death from trauma is higher in pediatric patients than in adult patients. Mechanisms of injury may be similar in adults and children, but children have particular anatomic differences and physiologic responses to injury. Health professionals should realize that children have unique anatomic and physiologic features compared with adults (Box 75.1). Evaluation and management of traumatized children requires specialized knowledge, training, and equipment. Recognition of such facts, coupled with expertise in the performance of emergency procedures, has improved the outcomes of children who sustain major injuries.

Epidemiology

Traumatic injuries are the most common cause of death in children aged 1 to 21 years (and in adults aged 21–44 years) in the United States. In many of these age groups, murder and suicide are the second and third leading cause of death, respectively. Approximately 7 to 8 million pediatric injuries result in 250,000 to 500,000 hospitalizations and 15,000 to 25,000 deaths each year. Medical costs associated with these injuries exceed $50 billion annually. Infants are most likely to die from suffocation, young children from drowning, school-age children from motor vehicle collisions or after being struck by an automobile, and adolescents from motor vehicle crashes. Boys are twice as likely as girls to be injured and die. The magnitude of pediatric trauma becomes even more evident when

Box 75.1. Characteristics of Children That Result in Increased Susceptibility to Injury

Anatomic

- Smaller body size allows for the greater distribution of force with trauma, so multisystem injury is common.
- A prominent occiput, exaggerated head-to-body ratio, weak neck muscles, and higher center of gravity predispose younger children to head injury.
- Cranial bones are thinner, and the brain is less myelinated, resulting in more serious head injury.
- Skeletal and ligamentous structures have increased flexibility, which results in greater transmission of force to internal organs.
- Less protective muscle and subcutaneous tissue over internal organs expose them to injury.
- Growth plates are not yet fused, which results in Salter-Harris-type fractures and possible bone growth abnormalities with healing.

Physiologic

- High body surface area-to-weight ratio predisposes children to hypothermia, which may complicate shock and worsen acidosis and coagulopathy if it is not corrected.
- Hypoxia and respiratory failure are more likely in children.
- Hemorrhagic shock is initially well tolerated by increasing heart rate and peripheral vascular resistance without significant changes in systolic blood pressure.

morbidity is considered. Between 50,000 and 100,000 children per year become permanently disabled as a result of their injuries. Such disabilities have an enormous effect on society; they result in financial and emotional losses for families and years of lost productivity for the injured individuals themselves.

Blunt trauma, which is more common than penetrating injury in children, represents approximately 87% of all childhood injuries. Head injuries, followed by thoracoabdominal injuries, are the leading causes of death in this group. In adolescents and young adults, however, penetrating injury (ie, homicide, suicide) accounts for a higher percentage of total trauma, especially among minority populations in urban areas. Causes of nonpenetrating trauma are motor vehicle crashes (>40%), falls (25%–30%), drowning (10%–15%), and burns (5%–10%). Included in the remainder are bicycle-related and automobile versus pedestrian injuries. These numbers vary significantly by locale and age. In some centers, a high percentage of trauma deaths are related to child abuse.

Clinical Presentation

Children who sustain severe trauma present with multiorgan system injury manifested by shock, respiratory failure, or altered mental status, either alone or in combination. Those with mild to moderate injury may present in this way or may simply present with localized signs and symptoms in the injured area.

Pathophysiology

It is important to identify patterns of injury to develop strategies for injury prevention as well as anticipate injuries during treatment. One common pattern is the *Waddell triad*, that is, the triad of injuries that results from an automobile versus pedestrian collision (Figure 75.1).

Multisystem injury is the rule rather than the exception in children. Internal injury must always be suspected when the mechanism of injury warrants such injury, even in the absence of apparent evidence suggestive of external trauma. Because children are anatomically and physiologically different from adults, they are more susceptible to diverse types of injury (see Box 75.1). The most striking physiologic differences between adults and children concern responses to acute blood loss. Children have a tremendous capacity to maintain systolic blood pressure despite 25% to 30% acute blood loss.

Hypovolemic shock secondary to acute blood loss is the most common cause of shock in pediatric trauma patients. *Hemorrhagic shock* is a clinical state in which cardiac output is unable to meet the metabolic demands of tissues for oxygen and nutrients; it is not defined by any absolute blood pressure value.

Acute blood loss stimulates peripheral and central receptors and results in increased production of catecholamines and corticosteroids. The body responds by increasing peripheral vascular resistance, stroke volume, and heart rate. Children have the capacity to dramatically increase heart rate and peripheral vascular resistance, and they often may exhibit normal blood pressure in the presence of hypovolemic shock. By the time their blood pressure falls, they commonly have lost 20% to 25% of their circulating blood volume. In adults, blood pressure tends to decline after a less significant blood loss, resulting in earlier recognition of the extent of blood loss (Figure 75.2). Subtle changes in heart rate, blood pressure, pulse pressure, and capillary refill may indicate impending cardiovascular collapse in children who have sustained traumatic injury and should not be overlooked. Indicators of end-organ perfusion, such as lactic acid levels or calculated base deficit, may also be helpful and predictive.

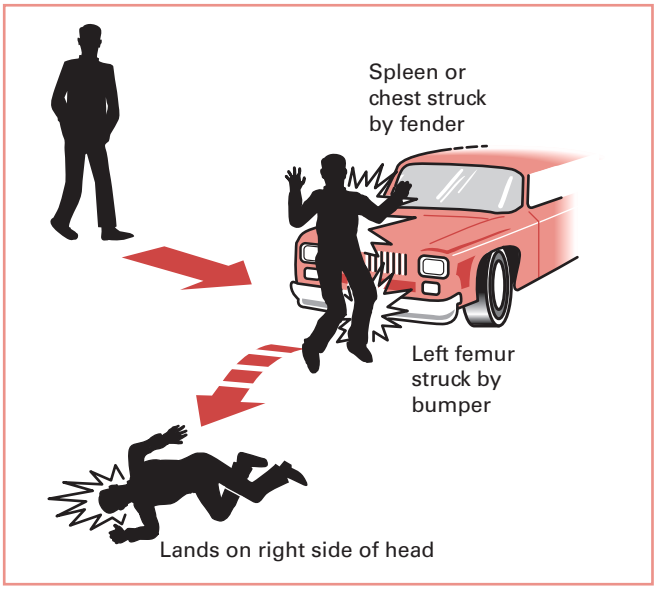

Figure 75.1. The Waddell triad, that is, femur, abdominal, and contralateral head injuries, should be expected to result from automobile versus pedestrian collisions in the United States. For example, a child crossing the street is struck on the left side of the body by an automobile traveling on the right side of the road. The left femur is likely to be injured by the bumper, and the abdomen or chest strikes the grille as the child is lifted into the air and lands on the opposite side of the head, sustaining blunt head trauma. The Waddell triad illustrates the necessity of having a high degree of suspicion for predictable injuries based on a well-known mechanism.

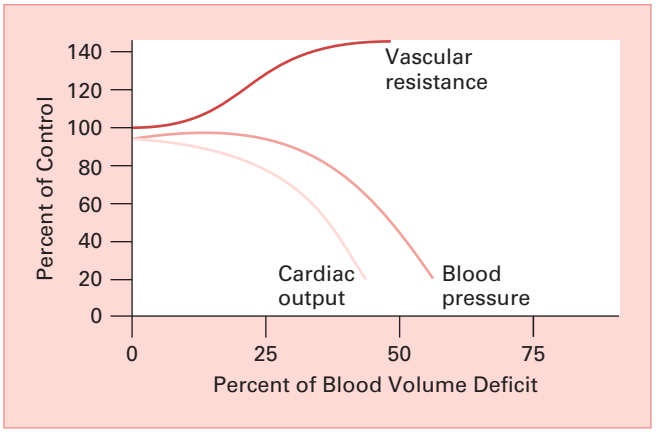

Figure 75.2. Cardiovascular response to hypovolemia in children. Blood pressure does not begin to decline until the volume deficit is more than 25% because of the compensatory increase in vascular resistance. Cardiac output drops earlier and is manifested clinically as delayed capillary refill; cool, clammy skin; and tachycardia.

Another obstacle to the recognition of shock in children is the lack of knowledge on the part of many health professionals of age-appropriate vital signs, particularly blood pressure. Table 75.1 gives the normal blood pressure ranges for children of different ages.

Three stages of shock correspond to the progression of volume loss. In the first stage, compensated shock, mechanisms for preserving blood pressure remain effective. Decreased capillary refill, diminished pulses, cool extremities, and tachypnea may be apparent, but blood pressure is normal (although accompanied by tachycardia). Unrecognized, untreated compensated shock rapidly progresses to uncompensated shock. Examination reveals decreased level of consciousness, pallor, reduced urine output, and lower blood pressure with weak, thready pulses and marked tachycardia. With inadequate therapy, uncompensated shock becomes irreversible shock, resulting in irreparable organ damage and often unpreventable death. (See Chapter 74 for a more extensive discussion.)

Shock has several causes, and it is important to emphasize that in trauma patients, it should always be initially attributed to hemorrhage. Shock resulting from obstructive cardiac output causes, such as tension pneumothorax or cardiac tamponade, is much less common. Shock resulting from spinal cord injury is exceedingly rare. Shock should never be attributed solely to head trauma. The pathways resulting in decreased blood pressure in patients with head trauma are present only at the terminal stages. Therefore, the possibility of blood loss from internal organs should be pursued promptly and aggressively. The most common site of hemorrhage resulting in preventable mortality is intra-abdominal. Other sources of hemorrhage are external, thoracic, pelvic, and retroperitoneal.

Evaluation and Management

Because of the high potential for serious morbidity and mortality in trauma patients, evaluation and management are performed simultaneously. This care is best managed using an organized, multidisciplinary team approach, with preestablished criteria for activation of the trauma team. History of the event provides important information when implementing these criteria. For example, the entire team responds for all pedestrians struck by an automobile. The types of subspecialists that make up a trauma team are decided by individual institutions and commonly include pediatric emergency and critical care specialists, anesthesiologists, trauma surgeons, surgical subspecialists, emergency nurses, respiratory therapists, social workers, and radiology technicians.

Several approaches to the assessment of trauma patients have been developed by professional organizations. The Advanced Trauma Life Support (ATLS) course of the American College of Surgeons and the International Trauma Life Support (ITLS) course (formerly Basic Trauma Life Support, which was initially funded by the American College of Emergency Physicians) are 2 such approaches. The ATLS and ITLS methods stress the importance of a primary evaluation, or primary survey, to identify and manage immediate life-threatening injuries followed by a more detailed regional examination, or secondary survey, after stabilization, to identify and manage all other injuries. Additionally, both protocols adhere to the principles of serial examination and reassessment after each intervention. The primary survey and initial resuscitation efforts must occur simultaneously and within the first several minutes of the evaluation. The secondary survey is meant to enhance the primary survey. Vital signs should be reassessed frequently during the primary and secondary survey until the trauma team feels the patient has been adequately stabilized. The physician should understand the rationale for the trauma examination and its parts. This topic is beyond the scope of this chapter, but articles that explain the rationale for trauma examination and provide detailed descriptions of evaluation and management techniques are listed in the Selected References section.

Physical Examination

The primary survey begins with an assessment of level of consciousness, patency of the airway (Box 75.2), and quality of breathing (Box 75.3). When evaluating injured patients, physicians should always assume that the cervical spine has been injured and should use in-line immobilization to secure it. Basic airway maneuvers for positioning should be performed, the safest of which is the jaw thrust to avoid moving the cervical spine (Figure 75.3). The oral cavity should be examined for foreign bodies, blood, or secretions. The most common form of airway obstruction in children is a posteriorly displaced tongue, which is relieved by good airway positioning. Advanced airway maneuvers (ie, bag-valve-mask ventilation, endotracheal tube intubation) are performed during the primary survey if the child has apnea, significant respiratory distress, severe head trauma, or an airway that cannot be maintained with basic

Table 75.1. Normal Vital Signs for Children by Age

Age	*Respiration (breaths/min)*	*Pulse (beats/min)*	*Blood Pressure (Systolic)*
Newborn	30–60	100–160	50–70
1–6 weeks	30–60	100–160	70–95
6 months	25–40	90–120	80–100
1 year	20–40	90–120	80–100
3 years	20–30	80–120	80–110
6 years	12–25	70–110	80–110
10 years	12–20	60–90	90–120

Box 75.2. Airway Assessment and Treatment

Assessment

- Airway patency and ability to protect it.
- Level of consciousness.
- Stridor.

Treatment

- Spinal immobilization.
- Jaw thrust and suctioning.
- 100% oxygen by non-rebreathing mask.
- Intubate for Glasgow Coma Scale score <9, or absence of an intact gag reflex.

Box 75.3. Breathing Assessment and Treatment

Assessment

- Respiratory rate and depth.
- Chest wall compliance, symmetry, and movement.
- Tracheal deviation.

Treatment

- 100% oxygen by non-rebreathing mask.
- Intubate for respiratory failure or severe flail chest.
- Compress obvious bleeding sites.
- Seal open pneumothorax with occlusive dressing.
- Needle decompression for tension pneumothorax.
- Place chest tube for pneumothorax or hemothorax.

Box 75.4. Circulation Assessment and Treatment

Assessment

- Identify obvious bleeding sites.
- Peripheral pulses and capillary refill.
- Heart rate.
- Level of consciousness.

Treatment

- Compress obvious bleeding sites.
- 100% oxygen by non-rebreathing mask.
- 2 large-bore intravenous lines.
- Fluid resuscitation with 20 mL/kg normal saline.
- Administer packed red blood cells at 10 mL/kg if after 60 mL/kg normal saline and patient still in shock.

techniques. All trauma patients are initially given supplemental oxygen by non-rebreathing mask at a concentration of 100%. The adequacy of ventilation is assessed by a general evaluation of the respiratory rate, depth, chest movement and symmetry, and tracheal deviation.

After a patent airway and adequate ventilation have been established, circulatory status is assessed. All pediatric trauma patients require placement of the largest bore intravenous catheter obtainable for that patient; these should be placed, if possible, in each antecubital fossa. Peripheral vascular access is attempted 3 times or for 90 seconds, whichever comes first. If peripheral attempts are unsuccessful, intraosseous infusion or central venous access should be used. A bolus of 20 mL/kg of an isotonic fluid (ie, normal saline or lactated Ringer solution) should be given. This may be repeated, if necessary, to manage hypovolemic shock. After 60 mL/kg, administration of 10 mL/kg of packed red blood cells should be considered if the patient is still in shock. The likelihood of surgical exploration is high. Acutely exsanguinating wounds are managed using direct pressure or tourniquet (Box 75.4).

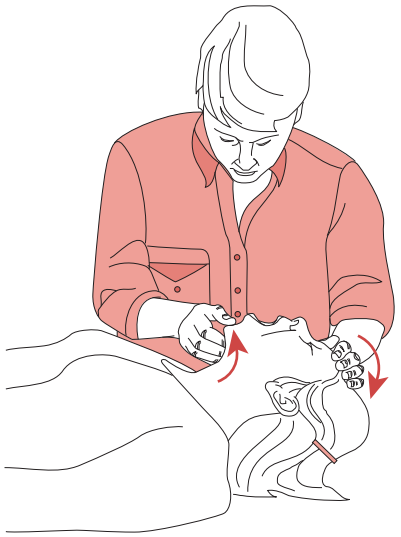

Figure 75.3. Correct method for positioning the head with chin lift or jaw thrust.

A brief neurologic assessment to assess patient disability is also performed during the primary survey. One rapid assessment technique is the AVPU system (alert; responds to verbal stimuli; responds to painful stimuli; unresponsive). Subsequently, a *Pediatric Glasgow Coma Scale* or *Children's Coma Scale* score should be calculated (Table 75.2).

After life-threatening conditions are stabilized, more information can be collected. The secondary survey involves a thorough head-to-toe examination of the child, fully exposed, to identify additional injuries, while taking great care to maintain normothermia. It also includes a SAMPLE (symptoms, allergies, medications, past history/hospitalizations/surgeries, last meal, events preceding trauma) history. A detailed history of events preceding trauma should ensure that injuries are consistent with the causal mechanism. Health professionals should be prepared to consider abuse when specific diagnoses do not correlate with the history given by the caregiver or the developmental ability of the child. Measurement of vital signs should occur as previously described and use of other devices, such as Foley catheters and nasogastric tubes, should be considered at this time. Each time an intervention is performed, repeat reassessments that incorporate the elements of the primary survey are made.

Laboratory Tests

Most institutions have a standardized trauma panel that is initiated for all patients, consisting of complete blood cell count with differential; assessment of electrolyte blood urea nitrogen, creatinine, glucose, and lactate levels; blood gas analysis with pH and base deficit; blood tests for amylase and lipase; liver function tests; assessment of prothrombin time and partial thromboplastin time; urinalysis; and blood typing and cross matching. Additionally, drug and alcohol screening may provide important information, particularly in the child with altered mental status. Female pediatric patients of potential childbearing age should undergo a point-of-care pregnancy test as well.

Imaging Studies

Sophisticated imaging techniques, such as ultrasonography and computed tomography, are a usual part of the evaluation of the seriously injured pediatric trauma patient. The choice of test depends

Table 75.2. Pediatric Glasgow Coma Scale

	>1 Year		< 1 Year	Score
Eye Opening	Spontaneously		Spontaneously	4
	To verbal command		To shout	3
	To pain		To pain	2
	No response		No response	1
Motor Response	Obeys		Obeys	6
	Localized pain		Localized pain	5
	Flexion-withdrawal		Flexion-withdrawal	4
	Flexion-abnormal (decorticate rigidity)		Flexion-abnormal (decorticate rigidity)	3
	Extension (decerebrate rigidity)		Extension (decerebrate rigidity)	2
	No response		No response	1
	>5 Years	*2-5 Years*	*0-23 Months*	
Verbal Response	Orientated	Appropriate words/phrases	Smiles/coos appropriately	5
	Disorientated/confused	Inappropriate words	Cries and is consolable	4
	Inappropriate words	Persistent cries and screams	Persistent inappropriate crying and/or screaming	3
	Incomprehensible sounds	Grunts	Grunts, agitated, and restless	2
	No response	No response	No response	1
			Total Pediatric Glasgow Coma Score (3-15)	

Reprinted with permission from Singh AP. Glasgow Coma Scale and Pediatric Glasgow Coma Scale. https://boneandspine.com/pediatric-glasgow-coma-scale.

on the experience of the trauma team and individual characteristics of the patient.

Point-of-care ultrasonography has become a routine part of the secondary survey in adult trauma patients. The extended focused assessment with sonography in trauma (e-FAST) examination seeks to detect intraperitoneal fluid (ie, hemoperitoneum), pericardial fluid (ie, hemopericardium), intrathoracic fluid (ie, hemothorax), and pneumothorax. The results are near instantaneous, and the examination may be done without moving the patient from the trauma bay. In critically unstable patients the e-FAST has great utility in directing the initial resuscitative efforts. The utility of e-FAST is less clear in the pediatric patient, but its use is supported, especially in the hemodynamically unstable patient.

When major trauma is suspected, computed tomography of the brain, cervical spine, chest, abdomen, and pelvis should be strongly considered after initial stabilization procedures are completed. This prevents missing injuries in children who may be unconscious or who need lifesaving procedures during resuscitation, which obscure an area of injury from examination. Additional radiographs of the extremities, for example, may be indicated when other areas of injury are detected on secondary survey. Children are often initially distracted from 1 injury because of the presence of a more painful injury.

Prevention

Mortality rates have changed little in the past several years even as trauma systems have matured and become widespread. Prevention strategies have become more important in reducing traumatic injury, but resources remain limited. Current pediatric prevention interventions are centered around reducing or preventing burns, drowning, falls, gunshot injuries, and poisoning as well as improving playground, road traffic, and sports safety.

Prognosis

Survival rates are highest for seriously injured children who are brought to the operating room for treatment within 1 hour of injury. Definitive care for trauma takes place in the operating room, and initial stabilization takes place in the emergency department. Absolute indications for surgery include hemodynamic instability despite aggressive resuscitation, transfusion of more than 50% of the total blood volume, pneumoperitoneum, intraperitoneal bladder rupture, severe renovascular injury, gunshot wounds to the abdomen, evisceration, and peritonitis. Other injuries, such as solid organ injuries, often in contradistinction to similar injuries in adult patients, are frequently treated more conservatively in the intensive care unit after complete consultation with all involved practitioners.

An organized, preestablished, multidisciplinary approach to care is essential. Studies have shown that the single most important element for any hospital treating injured children is the commitment on the part of the institution and its surgeons. Regional pediatric trauma centers have increased resources for managing severely injured patients that include long-term care and rehabilitation. Other nondesignated hospitals may do an excellent job in the initial stabilization phase of care. Indications for transfer to a specialty center include inability to provide definitive surgical intervention, inability to provide an appropriate intensive care environment, presence of multisystem injuries or injuries requiring extensive orthopedic

or plastic surgery procedures, and major burns. Health professionals who treat children should not only become adept in the recognition and initial stabilization of injuries but should also serve as advocates for injury prevention and coordinated prehospital care services in the community.

CASE RESOLUTION

The 6-year-old boy sustained multiple trauma from an automobile versus pedestrian collision. He presents with altered level of consciousness; respiratory failure (ie, shallow respirations); possible internal organ injury, which has the potential to result in shock; and probable fracture of the left femur, which may also contribute to the development of shock secondary to hemorrhage. These injuries are identified based on a primary and secondary survey. Proper management includes stabilization of the cervical spine, airway management, aggressive early shock treatment with fluid replacement, and a vigilant search for additional injuries. Continued reassessment is also an integral part of emergency department stabilization. Because of the presence of multisystem injuries, after initial stabilization the patient is transferred to a regional pediatric trauma center for extended care.

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CHAPTER 76

Abdominal Trauma

David B. Burbulys, MD

CASE STUDY

An 8-year-old boy who was riding downhill on a bicycle crashed into a tree and was transported to the local trauma center by emergency medical services. On arrival he was brought to the pediatric emergency department, where the paramedics report that the bike handlebars struck the child's abdomen. The boy reports dizziness and vomits several times. Initial vital signs show a heart rate of 135 beats per minute, blood pressure of 105/60 mm Hg, oxygen saturation of 98% on room air, and a respiratory rate of 24 breaths per minute. The abdomen is flat but tender to palpation in the mid-epigastric region and left upper quadrant.

Questions

1. What are the most common mechanisms of intra-abdominal injury in children?
2. What are the diagnostic studies used to evaluate abdominal trauma?
3. What is a simple rule for establishing the lower limit of normal blood pressure in children when assessing a child for shock?
4. What are the basic components of the treatment of shock that occur after abdominal trauma?

Abdominal trauma is the leading preventable cause of fatal injury in trauma patients. Death results when the extent and nature of abdominal injuries are neither appreciated nor appropriately managed, fluid replacement is inadequate, and airway maintenance and surgical intervention are not implemented soon enough. Primary abdominal trauma is the third leading cause of traumatic death, after head and thoracic injury. Clinicians should be knowledgeable about mechanisms of injury that result in abdominal trauma, early manifestations of shock, and methods of aggressive treatment of hemorrhagic shock.

Epidemiology

Twenty-five percent of children who sustain multisystem trauma have significant abdominal injury, and 9% die from abdominal-associated trauma. The risk of death is higher with simultaneous head and abdominal injury than with the occurrence of either injury alone. Blunt-force mechanisms are responsible for nearly 85% of abdominal injuries, with the remainder resulting from penetrating injuries. Examples of blunt-force mechanisms, presented in order of frequency from most to least frequent, include motor vehicle crashes, which also are the most lethal; pedestrian versus automobile collisions; falls; bicycle injuries; sports injuries; and direct blows from abuse and assault. Injuries to the spleen and liver predominate, followed by injuries to the kidney, bowel, and pancreas. In patients with multiple injuries, the incidence of trauma involving pelvic bones and organs (eg, bladder, ureter, iliac vessels) is also high. A straddle injury (eg, a fall that occurs when climbing over a fence) can also result in abdominal and pelvic trauma.

Clinical Presentation

Pain, tenderness, ecchymoses, and peritoneal signs (ie, voluntary or involuntary guarding, rebound tenderness) are among the more reliable signs of pathology, whereas abdominal distention and absence of bowel sounds are less consistent markers of injury. (See Box 76.1 for signs and symptoms suggestive of abdominal trauma.) It is particularly important to note that no sign is completely reliable and that acute hemorrhage into the abdomen does not result in peritoneal irritation initially. A high index of suspicion must be maintained in situations in which it is warranted based on the severity of the mechanism of injury, despite minimal initial physical findings. Unexplained hypotension or shock mandates further investigation with ultrasonography or computed tomography (CT) to assess for intra-abdominal hemorrhage.

Box 76.1. Signs and Symptoms Suggestive of Abdominal Trauma

- Pain
- Tenderness
- Distention
- Peritoneal signs (eg, absent or diminished bowel sounds, rebound tenderness, guarding)
- Ecchymoses
- Tire tracks
- Seat belt marks
- Urine, stool, or nasogastric aspirate positive for blood
- Unexplained hypotension or other signs of hypovolemic shock

Pathophysiology

Blunt trauma largely involves injury to solid, not hollow, intra-abdominal organs (ie, spleen and liver rather than small bowel) for a variety of reasons. First, the rib cage is flexible in children. As a result, rib fractures are less likely to occur, thereby reducing the potential for penetration of hollow abdominal organs by broken ribs. Second, children have less well-developed abdominal musculature and less adipose tissue than adults and larger organs relative to overall body size. Thus, in children blunt force is more easily and more diffusely transmitted to the solid organs. Third, because the diaphragm is oriented more horizontally in children than in adults, the liver and spleen lie more anteriorly and caudally within the abdomen.

It is important to emphasize that abdominal injury may result in excessive blood loss. The pathophysiology of hemorrhagic shock is discussed in detail in Chapters 74 and 75. The liver and spleen are highly vascularized organs that bleed profusely when lacerated. Even the accumulation of a subcapsular hematoma without rupture may cause a profound drop in hematocrit. Because intra-abdominal organs are not directly visible when a patient is examined, signs and symptoms of injury are not always obvious. Therefore, hemorrhagic shock should always be suspected in patients with abdominal trauma. Likewise, large volumes of blood can accumulate in the pelvis and retroperitoneum, and because of their proximity to the abdomen, they should always be considered as a reservoir for hemorrhage in abdominal as well as pelvic trauma.

Differential Diagnosis

Physicians should be familiar with the most common patterns of abdominal injury and should consider the possibility of specific injuries. Any solid abdominal organ can be injured by any mechanism, whether blunt or penetrating. The spleen is the most common intra-abdominal organ injured by a blunt force. Hepatic injuries are the most common fatal abdominal injuries, although they are less frequent than splenic injuries. The right lobe of the liver is injured more frequently than the left lobe.

Injuries to hollow viscera, such as the stomach and intestines, which represent only approximately 5% to 15% of injuries from blunt forces, are difficult to diagnose and often present late only after peritonitis manifests. Three mechanisms result in injury of hollow structures: "crush" between the anterior wall of the abdomen and the vertebral column; deceleration, which causes shearing of the bowel from its mesenteric attachments; and "burst," which occurs when an air- or fluid-filled loop of bowel is closed at both ends at the time of impact. Peritonitis may manifest within 6 to 48 hours secondary to fecal spillage or devascularization as the result of any of these mechanisms. Occasionally, a diagnosis of hollow viscera injury is made incidentally or may be delayed more than 48 hours, which reinforces the necessity of observation and serial examinations. Duodenal and pancreatic injuries are examples of potentially delayed diagnoses that can have grave consequences. Leakage of bile and enzymes may activate autolysis of the pancreas and result in sepsis syndrome.

Evaluation

Determining which organ or organs may be injured as the result of abdominal trauma is difficult. Up to 50% of significant injuries are missed on initial physical examination. Children are often uncooperative or unable to assist with the evaluation. Physicians tend to focus on injuries to the extremities, pelvis, face, or chest that are painful and distracting to children and more clinically obvious to the examiner. Initial clinical impressions may be incorrect, causing delayed diagnosis or unnecessary surgical exploration.

History

The history should focus on the mechanism of injury and the physiologic response of the child, especially in the pre-hospital setting (eg, initial hypotension, tachycardia, cyanosis; Box 76.2). A poor history concerning the circumstances of the injury may contribute to a delayed diagnosis.

Physical Examination

As stated previously, an abnormal physical examination may not always be indicative of pathology. Clinicians should avoid relying on physical examination alone as a predictor of abdominal injury. Studies have demonstrated that patients with and without proven injuries often showed no significant differences with respect to physical findings. In particular, children with abusive abdominal trauma often have no cutaneous evidence of bruising, especially immediately after the injury is inflicted (see Chapter 142). Thus, definitive evaluation of the abdomen is mandated for patients with significant mechanism of injury. Such evaluation often includes point of care ultrasonography, rapid CT, formal ultrasonography, diagnostic peritoneal lavage, laparoscopy, or laparotomy.

Vital signs should be monitored and trends followed. In children, the range for normal heart rate, respiratory rate, and blood pressure is age dependent. A simple rule for calculating the lower limit of normal systolic blood pressure is 70 + (2 × age in years). Physicians should always remember that a drop in blood pressure is a very late sign in the development of shock in children (see Chapters 74 and 75).

Serial abdominal examinations increase the likelihood of detecting a previously missed condition. Inspection of the abdomen to evaluate for ecchymoses, distention, tire tracks, penetrations, or paradoxical motion should occur first. Auscultation for bowel sounds follows this inspection, and palpation should be done last. Palpation should be done in all 4 quadrants to elicit tenderness, rebound, and

Box 76.2. What to Ask

Abdominal Trauma

- How was the child injured?
- How long ago did the injury occur?
- What parts of the body were injured?
- Did the child receive any treatment before coming to the hospital, and what was the response?

guarding. If a hepatic or splenic injury is initially suspected, palpation should be minimized to avoid further hemorrhaging.

Laboratory Tests

Laboratory evaluation should be guided by the history and physical examination. A urinalysis is helpful to evaluate for hematuria and associated genitourinary injuries. Elevated serum transaminases, amylase, lipase, and alkaline phosphatase may be indicative of injury; however, normal values do not exclude pathology. A comprehensive trauma panel, which usually includes a complete blood cell count and differential, serum electrolytes, blood urea nitrogen, creatinine, glucose, prothrombin time, partial thromboplastin time, blood gas analysis with pH and base deficit, lactic acid, and blood type and crossmatch as well, should be performed for all patients with serious or multiple injuries (see Chapter 75). Additionally, drug and alcohol screens may provide important information, particularly in children with altered mental status. Female patients of childbearing age also should undergo a point-of-care pregnancy test.

Imaging Studies

Multiple imaging modalities are available to assess the pediatric trauma patient with suspected abdominal injuries. The time to perform an imaging study is after the patient is responding appropriately to resuscitation (ie, fluid therapy). Unstable patients require surgical exploration for definitive treatment of abdominal or pelvic injury.

Computed tomography remains the standard of care for imaging the injured abdomen of a pediatric trauma patient. Computed tomography has greater than 97% accuracy in identifying abdominal or retroperitoneal injury, is noninvasive, and, most notably, provides detailed specific information about injuries. The images are also routinely extended to include the pelvis, as necessary. Disadvantages of CT may include the distance from the trauma suite, which may not be ideal for unstable patients; the length of time required to perform the procedure; the need for an intravenous contrast, which has inherent risks, such as allergic reactions and renal toxicity; and radiation exposure (see Chapter 17).

The use of point-of-care and formal ultrasonography has become quite popular, with encouraging results for the identification of abdominal injury, although its use in pediatric trauma patients remains somewhat controversial. Ultrasonography can be used to rapidly and noninvasively document the presence of intraperitoneal and pelvic fluid (ie, blood). Although ultrasonography is nearly as effective as CT for documenting the presence of injury, it does not provide as much specific information about the nature of the injury and does not image the retroperitoneal space. Ultrasonography has a few additional advantages. It is relatively inexpensive; does not require contrast or radiation exposure; can be performed in minutes in the trauma room, thus minimizing the risk to an unstable patient; and can be used many times for serial assessments.

Although for several decades diagnostic peritoneal lavage was a dependable method of detecting intra-abdominal hemorrhage, its use has been largely replaced by ultrasonography, and it has limited use in the pediatric population because currently, many children with blunt trauma to the abdomen are often treated nonsurgically.

Management

Management of abdominal trauma in children occurs simultaneously with evaluation. The stabilization of children with abdominal trauma, especially in the context of multiple trauma, requires a multidisciplinary team approach that includes surgeons, pediatricians, and emergency physicians. A discussion on approach to trauma management can be found in Chapter 75.

Hypovolemic shock, if present, is the primary complication of abdominal trauma on which to focus, because the leading unrecognized cause of death in affected children is profound blood loss. Airway problems and breathing difficulties should be addressed initially, followed by vascular access and fluid replacement. No more than 3 attempts at peripheral vascular access should be made within 90 seconds before proceeding to more invasive procedures.

The intraosseous route should be used for the next vascular access attempt. The flat, medial portion of the proximal tibia is most commonly used for the procedure, which is performed with an intraosseous, bone marrow, or spinal needle (Figure 76.1). Fluids and medications delivered into the marrow cavity flow into the venous circulation. Intraosseous cannulation is rapid and simple and may be lifesaving. It is limited by low flow rates (approximately 30 mL/min), which can be augmented by using pressure on the intravenous bag or by pushing fluid by hand through a syringe. Complications associated with intraosseous line placement are rare. All physicians who care for pediatric trauma patients should be familiar with this technique.

A variety of central venous access sites, such as femoral, subclavian, and internal jugular, may be used in older children. The Seldinger technique, with insertion of a large-bore catheter over a guidewire, is often used. Intravenous access above the diaphragm is preferred in patients with blunt or penetrating abdominal trauma who have the potential for disruption of the vena cava or other large veins.

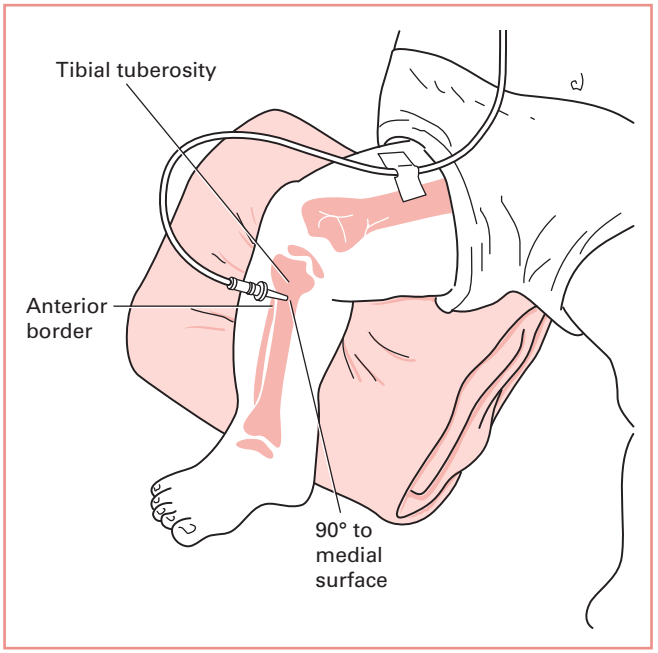

Figure 76.1. Intraosseous cannulation technique.

Fluid replacement begins with a 20 to 40 mL/kg bolus of crystalloid solution (warmed normal saline or lactated Ringer solution). If no improvement in circulation occurs, additional 10 to 20 mL/kg boluses may be given, and type-specific packed red blood cells should be considered. In most scenarios, type-specific blood is given after 60 mL/kg of crystalloid has failed to improve circulatory parameters. Frequent hematocrits or hemoglobins should be determined to monitor ongoing blood loss. Vital signs should be repeated frequently. Serial examinations, which detect the signs and symptoms of shock (Box 76.3), are the most important gauge of hemodynamic recovery and stability. All children require close hospital observation, preferably in a pediatric trauma center and pediatric intensive care unit.

Orthostatic fall in blood pressure and supine hypotension (late sign) must be aggressively managed. If hemodynamic stabilization is not achieved after appropriate vascular access and fluid resuscitation, the trauma surgeon will most likely perform an exploratory laparotomy. If the child has been stabilized with initial airway and circulatory support, diagnostic procedures (eg, CT) can be performed as part of the emergency department evaluation. Once identified, specific organ injury can be managed.

Other specific management concerns for pediatric patients with abdominal injury are early decompression of the stomach with a nasogastric or orogastric tube to prevent respiratory compromise and urinary catheter insertion to decompress the bladder. Before inserting a urinary catheter, the trauma team should evaluate for possible urethral trauma and check for the presence of blood in the urine, which may indicate other genitourinary trauma.

Nonsurgical management of minor to moderate liver or spleen injuries is common in children. A watchful waiting approach is often used after hemodynamic stability has been achieved. More severe injuries, including bowel rupture, require surgical intervention.

For injuries not requiring truly emergent surgical intervention, interventional radiology-guided arterial embolization has become a useful tool for significant liver, spleen, and kidney injuries, as well as pelvic fractures.

Prognosis

Morbidity and mortality related to abdominal trauma depend on the specific organ injury and style of management. Up to 40% of patients with major liver injuries die. However, several less severe liver injuries can be managed without surgery. Currently, an increasing number of injuries to the spleen and liver are managed with observation in the pediatric intensive care unit. Surgical exploration and repair are performed only if patients become hemodynamically unstable. Reduction in anesthesia-related mortality, postsplenectomy sepsis, and other postoperative complications have resulted from this shift in practice style. Without surgical intervention, however, a severe injury such as complete splenic rupture has a 90% to 100% mortality rate.

Box 76.3. Signs and Symptoms of Hemorrhagic Shock in Children

- Anxiety, irritability, decreased responsiveness
- Cool and mottled skin, pallor
- Delayed capillary refill (>2 seconds)
- Respiratory distress
- Tachycardia
- Thirst

CASE RESOLUTION

The boy sustained isolated abdominal trauma. Initial presenting signs and symptoms are concerning for internal organ injury, specifically splenic hematoma, pancreatic injury, internal hemorrhage, and compensated shock (eg, tachycardia, tachypnea). The child is managed with standard initial resuscitation, including fluid repletion. Because serial hemodynamic measurement and hematocrits are stable, he undergoes an abdominal CT scan, which demonstrates a splenic hematoma. A pediatric surgeon is consulted and recommends observation with continued monitoring in the pediatric intensive care unit.

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CHAPTER 77

Acute Abdomen (Appendicitis)

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CASE STUDY

A 10-year-old girl presents with abdominal pain of 24 hours' duration. The pain began in the periumbilical area and now is located in the right lower quadrant. She had 1 bout of emesis but no diarrhea. She has no fever or chills. She also has some pain with voiding. On physical examination, she has a low-grade fever and tachycardia. She is lying still in bed. Her abdomen is nondistended, but she has tenderness to palpation in the right lower quadrant. She also has rebound tenderness and guarding in this area.

Questions

1. What is the differential diagnosis for patients with acute abdominal pain?
2. What is the appropriate workup for children with suspected appendicitis?
3. What is the current management for children with appendicitis?
4. What is the expected postoperative course and possible complications following appendectomy?

Appendicitis is among the most common surgical emergencies in children. Pediatricians play a key role in the diagnosis and management of patients with abdominal pain and must be able to distinguish appendicitis from other causes of abdominal pain. When a patient presents with the classic signs and symptoms of appendicitis, the diagnosis is simple. Unfortunately, approximately 50% of patients present with atypical signs and symptoms of appendicitis, making the diagnosis difficult. Until recently, nearly every aspect of the diagnosis and management of children with appendicitis has been controversial. Thus, it is important for primary care physicians, emergency department physicians, and surgeons to communicate effectively to provide the highest level of care and cost efficiency.

Epidemiology

More than 70,000 children are affected by appendicitis each year in the United States. The lifetime risk of appendicitis is 9% in boys and 7% in girls.

Pathophysiology

The 2 main causes of abdominal pain are distention of the viscera, causing visceral pain, and irritation of the peritoneum, causing somatic pain. Distention of any hollow organ in the abdomen causes crampy and intermittent abdominal pain. Examples include distention of the biliary tree, small or large intestine, urinary structures (ie, bladder, ureters), or gynecologic structures (ie, uterus, fallopian tubes). This visceral pain is poorly localized and tends to be reported in the midline. Distention of any foregut structure localizes to the epigastric region. Foregut structures derive their blood supply from the celiac trunk and include the stomach, duodenum, and biliary tree. Distention of midgut structures localizes to the periumbilical region, and distention of hindgut structures localizes to the suprapubic region. Midgut structures are supplied by the superior mesenteric artery (ie, duodenum to transverse colon) and hindgut structures by the inferior mesenteric artery (ie, transverse colon to rectum). Unlike visceral pain, somatic pain is well localized. Irritation of the parietal peritoneum results in sharp pain and localized tenderness on examination. Anything that causes the irritated peritoneum to move or stretch worsens the pain and tenderness.

The classic example of these 2 types of pain occurs with appendicitis. The basic pathophysiology of appendicitis is obstruction of the lumen of the appendix followed by infection. Obstruction may be caused by fecal material (ie, appendicolith, fecalith), lymphoid hyperplasia, foreign body, tumor, or parasites. Following obstruction, the appendix becomes distended from accumulation of mucus and proliferation of bacteria. This distention results in a vague periumbilical pain. As intraluminal pressure increases, lymphatic and venous drainage are impaired, resulting in edema of the appendicular wall. As the overlying parietal peritoneum becomes progressively more irritated, the pain localizes to the right lower quadrant (RLQ). This stage is known as *acute appendicitis*. Further increase in pressure limits arterial inflow and ultimately results in tissue necrosis and perforation. Although the natural history of untreated appendicitis is usually perforation and abscess, not all patients progress to perforation.

Clinical Presentation

Abdominal pain is the most common symptom of and is present in nearly every patient with appendicitis. The classic presentation of a child with appendicitis includes a history of initial periumbilical

pain migrating to the RLQ. The pain is gradual in onset and progressively worsens. Anorexia, nausea, and vomiting typically are associated with appendicitis. In most cases, these associated symptoms manifest after the onset of abdominal pain. Intermittent, crampy pain that manifests after the onset of vomiting or diarrhea is less commonly associated with appendicitis. The inflamed appendix irritates the overlying peritoneum by direct contact, which results in focal peritonitis and localized RLQ pain. The symptoms vary based on the location of the appendix, however. When the appendix is retrocecal, a dull ache is often described. When the tip of the appendix is located in the pelvis, atypical pain is described. A child may report dysuria and urinary frequency resulting from the inflamed appendix irritating the bladder. Diarrhea or tenesmus may occur if the appendix is adjacent to the rectum. Fever, tachycardia, and leukocytosis occur as a consequence of systemic inflammatory mediators released by ischemic tissues, white blood cells, and bacteria. Higher fevers are associated with perforated appendicitis.

Box 77.1. What to Ask

Abdominal Pain

- When did the pain start?
- Can you describe the nature of your pain?
- Is your pain constant or intermittent?
- Where is your pain?
- What makes your pain worse? Better?
- Do you have any fever or chills?
- Do you have any nausea, vomiting, or diarrhea?
- When was your last bowel movement?
- Do you have any pain with urinating?
- Are you hungry?
- When was the last time you ate? Drank?
- Have you had any ill contacts?
- Have you had any upper respiratory symptoms?

Differential Diagnosis

Acute appendicitis can mimic nearly any intra-abdominal process and should be high on the differential in all children who report abdominal pain. Other causes of RLQ pain that are often indistinguishable from acute appendicitis include mesenteric adenitis, viral gastroenteritis, regional bacterial enteritis, tuboovarian pathologic processes, inflammatory bowel disease, Meckel diverticulum, cecal diverticulitis, and constipation. Other causes of lower abdominal pain include urinary tract infection, kidney stone, uterine pathologic process, bowel obstruction, and malignancy (eg, lymphoma). Vague abdominal pain can be caused by right lower lobe pneumonia, sigmoid diverticulitis, pancreatitis, hepatitis, and cholecystitis.

Evaluation

History

A careful history is required to distinguish acute appendicitis from other causes of abdominal pain (Box 77.1). In most patients with acute appendicitis, pain is often the first symptom. Associated symptoms, such as nausea, vomiting, and diarrhea, present after the onset of pain. It is important to distinguish intermittent crampy pain from constant and progressively worsening pain. If the patient has nausea, vomiting, or diarrhea followed by intermittent crampy pain, the diagnosis of gastroenteritis is more likely than appendicitis. A patient may develop a low-grade fever within 24 hours of the pain. Higher fevers manifest later and occur more frequently with perforated appendicitis. For the patient in whom fever is the first sign or symptom, appendicitis is less likely.

Physical Examination

A thorough physical examination is necessary to rule out other causes of abdominal pain. Upper respiratory infections may result in mesenteric adenitis, causing abdominal pain. The patient with acute appendicitis usually lies still, because movement worsens the pain. The most common finding is focal tenderness in the RLQ. Applying pressure to a stethoscope while listening to the abdomen is a subtle means of palpating the abdomen in the frightened child in whom it is difficult to obtain an accurate examination. Because of the level of discomfort, it may be difficult to elicit rebound tenderness and palpate for a mass. Asking the child to walk or jump is an easier and more accurate method of determining the degree of peritoneal irritation. Narcotic analgesics improve patient comfort but do not alter the inflammatory process; thus, tenderness persists. Localized tenderness is dependent on peritoneal irritation; thus, obesity, a retrocecal appendix, or walling off of the appendix by the omentum, mesentery, or small bowel may make the diagnosis of appendicitis more challenging.

Laboratory Tests

Laboratory studies often show a mild leukocytosis. A markedly elevated leukocyte count is suggestive of perforation or another diagnosis. A "shift to the left" in the complete blood count and differential may be a better diagnostic indicator for appendicitis. Other inflammatory markers, including C-reactive protein, procalcitonin, and lactic acid, have also been investigated but have not been routinely used in the workup of patients with suspected appendicitis. A urinalysis should also be obtained and usually is free of bacteria; however, a few or moderate number of red or white blood cells may be found because the inflammatory process of the appendix may cause localized irritation of the bladder or ureter.

Imaging Studies

Appropriate use of diagnostic imaging can minimize negative appendectomy and perforation rates.

Plain Radiography

In general, plain radiographs of the abdomen and chest may be more useful to evaluate for other disease processes when the suspicion

for appendicitis is low. Specific to appendicitis, plain radiography can show fecaliths in 10% to 20% of patients. Other helpful findings include lumbar scoliosis and obliteration of the psoas shadow.

Ultrasonography

Ultrasonography is an efficient bedside study that is noninvasive, requires no contrast, and emits no radiation. It should be the first study used in the workup of the patient with suspected appendicitis. Common ultrasonography findings consistent with appendicitis include a fluid-filled, noncompressible tubular structure; a diameter greater than 6 mm; appendicolith; and periappendicular or pericecal fluid (Figure 77.1). With an experienced technician and in the ideal situation, ultrasonography has sensitivity greater than 85% and specificity greater than 90%. Results are also influenced by patient factors, such as bowel gas pattern, obesity, and guarding or movement. When a normal appendix is identified, ultrasonography is a reliable study to rule out appendicitis. Only 10% to 50% of children with a normal appendix can be identified, however. Furthermore, when the appendix is not identified a risk for appendicitis remains despite otherwise normal ultrasonography findings.

Computed Tomography

When appendicitis cannot be excluded or confirmed on ultrasonography, additional imaging with computed tomography (CT) or observation is warranted. Findings consistent with appendicitis on CT include an enlarged appendix (>6 mm), appendicular wall thickening (>1 mm), periappendicular fat stranding, and appendicular wall enhancement (Figure 77.2). Computed tomography has a sensitivity and specificity of approximately 95%. Several concerns exist with CT, however. Significant delay in obtaining the study may occur if oral contrast is administered; the younger child may require sedation to complete the study; and growing concern exists for the increased radiation exposure from CT (see Chapter 17). Developing tissues have increased sensitivity to the effects of radiation, as evidenced by an increased risk of radiation-induced malignancy in patients exposed at a younger age.

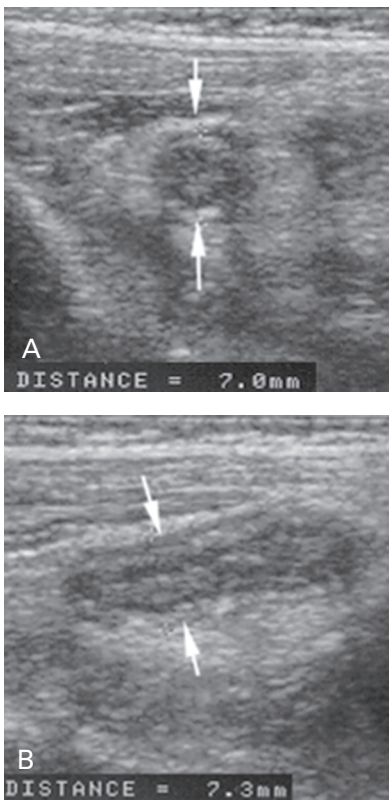

Figure 77.1. Sonograms consistent with acute appendicitis. A, Transverse view. B, Longitudinal view. In both images, the arrows are used to measure the diameter of the appendix.

Magnetic Resonance Imaging

Magnetic resonance (MR) imaging has a high diagnostic accuracy similar to CT and can be used to diagnose acute appendicitis in lieu of CT. Findings on MR imaging that are consistent with acute appendicitis include an enlarged (>6 mm), curved, and thickened blind-ended and fluid-filled tubular structure that is markedly enhanced on contrast-enhanced T1-weighted imaging (Figure 77.3). Magnetic resonance imaging has several advantages compared with CT, such as lower radiation exposure, which is particularly beneficial in the pediatric population. Additionally, MR imaging affords better visualization of an acutely inflamed and/or abnormally located appendix than ultrasonography. However, MR imaging is much costlier than ultrasonography and CT, patients must remain still for longer periods of time, it is not well suited for patients with claustrophobia, and it is not readily available at many institutions.

Observation

When appendicitis cannot be excluded or confirmed based on the history, physical examination, laboratory studies, and ultrasonography, additional imaging (ie, CT or MR imaging) or observation is indicated. Given the radiation risks associated with CT and the limited availability of MR imaging, admission to the hospital for intravenous (IV) fluids and serial examinations is a safe alternative. Food and liquids should be withheld, and a repeat complete blood cell count with manual differential should be obtained the next morning. In most instances, patients who do not have appendicitis improve and can safely be allowed to eat and discharged home. In children with appendicitis the pain will increase, and IV antibiotics should be administered while arrangements for appendectomy are made.

Management

The management of appendicitis begins with IV fluids and broad-spectrum IV antibiotics. Single- or double-agent therapy has been shown to be as effective as and more cost-efficient than triple-agent antibiotics. Management after initiating antimicrobial therapy is based on whether the patient is likely to have nonperforated or perforated appendicitis. This distinction is not always clear, even if preoperative imaging studies have been obtained. For the patient presenting with symptoms that have been present for less than 24 hours, the risk of perforated appendicitis is low. These patients

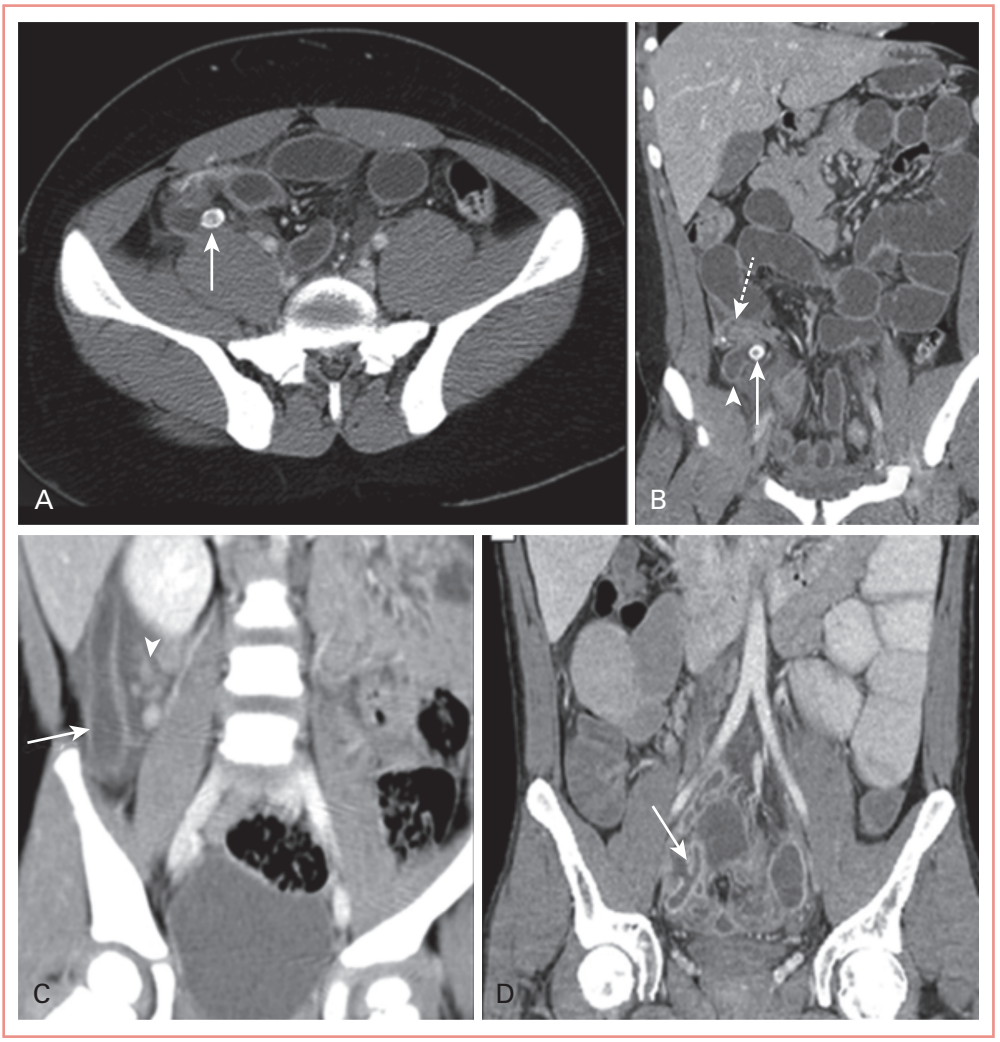

Figure 77.2. **Computed tomography images consistent with appendicitis. A, an axial view showing an appendicolith (arrow). B, a coronal view showing an appendicolith (arrow), periappendiceal inflammatory changes (dashed arrow), and an inflamed appendix (arrowhead). C, a coronal view showing an inflamed appendix (arrow) and an inflamed lymph node (arrowhead). D, a coronal view showing an inflamed appendix (arrow).**

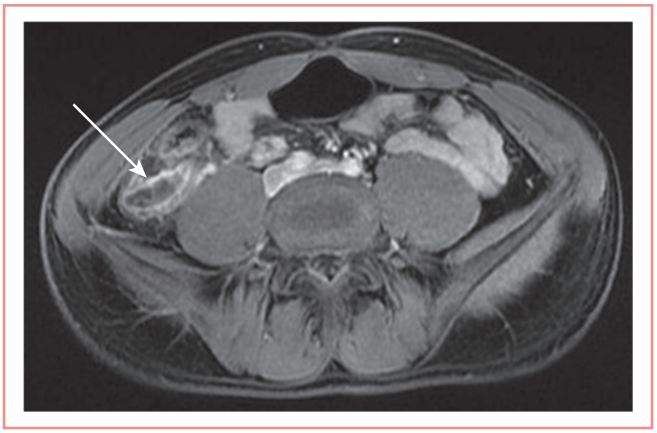

Figure 77.3. **Axial magnetic resonance image used to diagnose acute appendicitis (arrow).**

should be adequately resuscitated with IV fluids and antibiotics and scheduled for appendectomy at a later time. Antibiotic therapy typically halts or even reverses disease progression. Thus, the likelihood of nonperforated appendicitis progressing to perforated appendicitis is highly unlikely after appropriate antibiotics have been started. For this reason, appendectomy may be considered a semielective procedure rather than an urgent or emergent procedure as it has historically been considered. Duration of symptoms longer than 24 hours is associated with increased risk for perforation. In most instances, the patient with symptoms lasting fewer than 5 to 7 days is treated as described previously.

The patient with symptoms lasting more than 7 days likely has perforated appendicitis with or without an abscess. In the patient with prolonged duration of symptoms, appendectomy can be more technically challenging and associated with an increased rate of postoperative complications.

Nonsurgical management has been done in an attempt to reduce these risks. Nonsurgical management includes administration of IV antibiotics and drainage of intra-abdominal abscess (if present) using interventional radiologic techniques. Initial nonsurgical management is successful in approximately 85% of patients. Historically, after a patient was clinically stable the individual was discharged and elective interval appendectomy was typically performed 6 to 8 weeks later. Recent studies, however, indicate that an interval appendectomy may not be indicated for most patients unless symptoms recur. If nonsurgical management is unsuccessful, appendectomy is performed.

Charles McBurney, MD, first described open appendectomy through a traditional RLQ incision and muscle-splitting technique in 1893. Laparoscopic appendectomy was introduced more than 30 years ago and has largely replaced open appendectomy. Compared with the open technique, laparoscopic appendectomy is associated with lower wound infection rates, shorter hospital stay, fewer postoperative outpatient visits, and earlier return to routine activity. Although earlier studies associated laparoscopic appendectomy with higher postoperative abscess rates and longer duration of operation compared with the open technique, more recent studies show no difference in these areas. In fact, some studies have shown shorter surgical time and lower abscess rates with laparoscopic appendectomy.

Primary nonsurgical management of acute appendicitis, without the intention of eventual appendectomy, recently has been gaining in popularity and appears to be a clinically effective, cost efficient, and safe approach. Currently, primary nonsurgical management is reserved for uncomplicated appendicitis. After diagnosis, several doses of IV antibiotics are administered, followed by a 7- to 10-day course of oral antibiotics. To date, no standardized consensus antibiotic regimen exists. The presence of an appendicolith is associated with a high initial failure rate of nonsurgical management, and appendectomy is recommended in these cases. Currently, the initial success rate of nonsurgical management is 90% to 95%, with a recurrence rate of approximately 20% at 1-year follow-up. Thus, the overall success rate at 1 year is 75%. Patients who return with a recurrence of their symptoms do not typically experience a perforation, but appendectomy is recommended.

For the patient with nonperforated appendicitis undergoing appendectomy, antibiotics are administered for a maximum of 24 hours and typically are not necessary postoperatively. A single preoperative dose of antibiotics has been shown to decrease the risk of wound infection and abscess. For the patient with perforated appendicitis, IV antibiotics should be administered until resolution of clinical symptoms, including resolution of fever, normalization of physical examination, and full return of gastrointestinal function. If this duration of IV antibiotic therapy is for fewer than 5 days, the patient can be safely discharged on oral antibiotics to complete a 7-day course.

Prognosis

Overall complication rates are less than 3% for nonperforated appendicitis and 16% to 18% for perforated appendicitis. The common complications after appendectomy are infection related. Wound infection occurs in less than 1% of patients with nonperforated appendicitis and up to 16% of patients with perforated appendicitis. Rates of postoperative abscess are less than 1% for nonperforated appendicitis and less than 15% for perforated appendicitis. Mortality related to appendicitis is rare.

CASE RESOLUTION

The patient was found to have an elevated white blood cell count with a shift to the left and a small number of white blood cells in the urinalysis. Ultrasonography findings were consistent with acute appendicitis. She was administered IV fluids and antibiotics and underwent laparoscopic appendectomy. The postoperative course was unremarkable, and the patient was discharged the next day. She did well in follow-up and was cleared for full activity 2 weeks postoperatively.

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CHAPTER 78

Head Trauma

Joseph Ravera, MD

CASE STUDY

A 2-year-old girl is playing on a window ledge unsupervised. She pushes the screen out and falls onto the concrete sidewalk below, striking her head. A neighbor reports that she is unconscious for 10 minutes. When paramedics arrive, the girl is awake but lethargic. She is transported to the emergency department. Her vital signs are normal. A scalp hematoma is present, and a depressed area of cranial bone is palpated.

Questions

1. What are the priorities in the initial stabilization and management of pediatric head trauma?
2. What is the difference between primary and secondary brain injury?
3. What are the common signs and symptoms manifested by children with head trauma?
4. What are the various modalities available for management of increased intracranial pressure?
5. What are the scoring systems used in the evaluation of mental status in children with head trauma?

Although most childhood head injuries are minor and can be managed on an outpatient basis, it is important for physicians to become adept at recognizing and managing concussions and more severe forms of head injury. Health professionals can also help reduce mortality from head trauma by actively promoting injury prevention to patients and communities.

Epidemiology

Head trauma is among the most common pediatric injuries and the leading cause of morbidity and mortality among pediatric trauma patients. Pediatric head trauma accounts for more than 500,000 emergency department (ED) visits, 95,000 hospital admissions, 7,000 deaths, and 29,000 permanent disabilities per year in the United States. Hospital care costs exceed $1 billion annually. In pediatric patients with multiple injuries, 70% of deaths that occur within 48 hours of hospitalization are the result of trauma to the head. Rates of intracranial injuries in children with only minor head trauma are low, however, with the largest numbers occurring in young children and infants, with a prevalence of 3% to 6%. Only 0.4% to 1% of children require surgical intervention after minor closed head injury.

Falls account for most cases of pediatric head trauma. Other major causes include motor vehicle crashes, vehicle versus pedestrian collisions, bicycle crashes, sports-related injuries, and recreational activities. Nonaccidental trauma (ie, child abuse) must be recognized as another important cause of head injury in children, particularly among those younger than 2 years.

Clinical Presentation

The child who has sustained head trauma may present with a history of an antecedent event (eg, fall, collision with another child) or signs and symptoms related to the injury. These include external bruising or lacerations, alterations in the level of consciousness, and neurologic findings, including seizure. Vital signs may be altered; in particular, deep or irregular respirations, hypertension, or bradycardia may be apparent (Box 78.1). These changes are indicative of elevated intracranial pressure (ICP).

Pathophysiology

Children have significant anatomic differences from adults that predispose them to head trauma and certain types of intracranial

Box 78.1. Diagnosis of Head Trauma[a]

- Loss of consciousness
- Somnolence
- Pallor
- Emesis/nausea/anorexia
- Irritability
- Lethargy
- Seizure
- Ataxia
- Weakness
- Pain
- Paresthesias
- Amnesia
- Headache
- Visual changes
- Confusion/altered mental status

[a] All symptoms need not be present for a diagnosis of head trauma.

injury (Figure 78.1). They have a higher center of gravity, an increased head to body ratio, and weaker neck muscles compared with adults. Additionally, children have thinner cranial bones and less myelinated brain tissue, which predisposes them to intraparenchymal injuries. Whereas adults are more likely to have focal intracranial hematomas, children are more likely to develop diffuse cerebral edema. Cerebral edema can disrupt cerebral blood flow, resulting in ischemic injury.

Normally, blood flow to the brain is maintained at a constant rate by the process of *autoregulation*. With severe brain injury, autoregulation is disrupted and blood flow to the brain is determined by cerebral perfusion pressure (CPP), which is a measure of the mean arterial pressure (MAP) less ICP (CPP = MAP – ICP). Cerebral blood flow is therefore compromised when the MAP is too low (ie, hypotension) or the ICP is too high (ie, cerebral edema). Several of the management strategies in children with severe brain injuries focus on maintaining MAP and reducing ICP; however, control of CPP after head injury can be quite difficult. Children have a greater capacity for recovery than adults; this is especially true for infants and very young children, whose open sutures and fontanels permit expansion of the skull in response to edema and blood.

In head trauma, primary and secondary brain injury can occur. Primary injury is the structural damage that occurs to the cranium and its contents at the time of injury. Secondary injury is damage to the brain tissue after the initial event. Such damage may result from hypoxia, hypoperfusion, hypercapnia, hyperthermia, and altered glucose or sodium metabolism. The main treatment strategies for patients who have sustained head trauma focus on the prevention of secondary brain injury. Primary brain injury can be prevented only through education and safety, such as advocating for wearing helmets in appropriate situations.

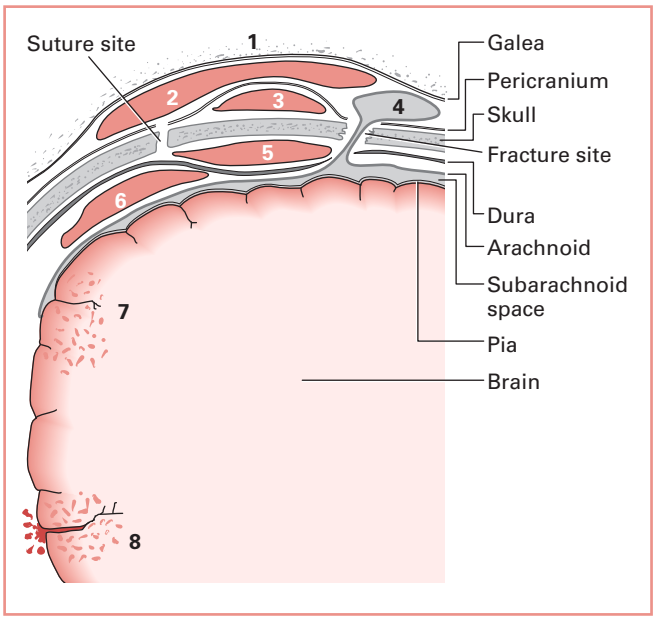

Figure 78.1. Functional anatomy of the brain and surrounding structures with sites of pathology. 1, Caput succedaneum. 2, Subgaleal hematoma. 3, Cephalhematoma. 4, Porencephalic or arachnoid cyst. 5, Epidural hematoma. 6, Subdural hematoma. 7, Cerebral contusion. 8, Cerebral laceration.
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Types of Head Injury

Even minor head trauma in a child can result in skull fracture or intracranial injuries. Most skull fractures are simple and linear. Other fracture types are comminuted, diastatic, basilar, and depressed. A *comminuted fracture* is one involving multiple skull fragments. A *diastatic fracture* is one with a wide separation at the fracture site. *Basilar fractures* occur at the base of the skull and often have characteristic findings on physical examination (ie, bilateral periorbital ecchymosis [ie, raccoon eyes], hemotympanum, postauricular ecchymosis [ie, Battle sign]). In a *depressed fracture*, fragments of the skull are displaced inward, potentially damaging intracranial structures.

Head trauma may result in concussion, mild traumatic brain injury, or intracranial hemorrhage. A *concussion* is defined as a trauma-induced impairment of neurologic function. This may occur with or without a loss of consciousness (LOC). Neurologic examination is usually normal, but the patient may experience somatic symptoms (eg, headache), physical signs (eg, LOC, amnesia), behavioral changes, cognitive impairment, or sleep disturbances. Some of these minor and subtle neurologic sequelae can last for months after the injury (ie, postconcussion syndrome). Most resolve within a relatively short period, typically 7 to 10 days; however, with more severe trauma the symptoms can last longer.

A *cerebral contusion* is a bruise of the brain tissue and typically occurs with a more severe injury, such as a high-speed motor vehicle crash. A *contrecoup contusion* may be sustained when the brain strikes the skull on direct impact, bruising 1 portion of the brain, with resulting injury to the opposite side of the brain on rapid deceleration. Clinical manifestations depend on the location of the contusion but often include altered mental status, excessive sleepiness, confusion, and agitation. Small intraparenchymal hemorrhages and swelling of the surrounding tissues are often seen on computed tomography (CT).

An *epidural hematoma* is a collection of blood that accumulates between the skull bone and the tough outer covering of the brain (ie, dura mater). These are often the result of tears in the middle meningeal artery caused by skull fractures. Classically, patients have initial LOC followed by a lucid interval and then rapid deterioration secondary to brain compression. On CT, an epidural hematoma appears as a large collection of blood with convex borders next to the skull (Figure 78.2A). Surgical evacuation is required in most cases.

The *subdural hematoma* accumulates between the dura and the underlying brain tissue. These are associated with skull fractures and contusions. On CT, they appear to have a crescent-shaped border (Figure 78.2B). Large subdural hematomas usually require surgical evacuation. In infants and young children, subdural hematomas are often the result of nonaccidental trauma.

Diffuse axonal injury (DAI) involves extensive damage to the axonal white matter of the brain that results from shearing forces that typically occur with rapid acceleration or deceleration of the brain (Figure 78.2C). The child with DAI may have normal or nonspecific findings on CT.

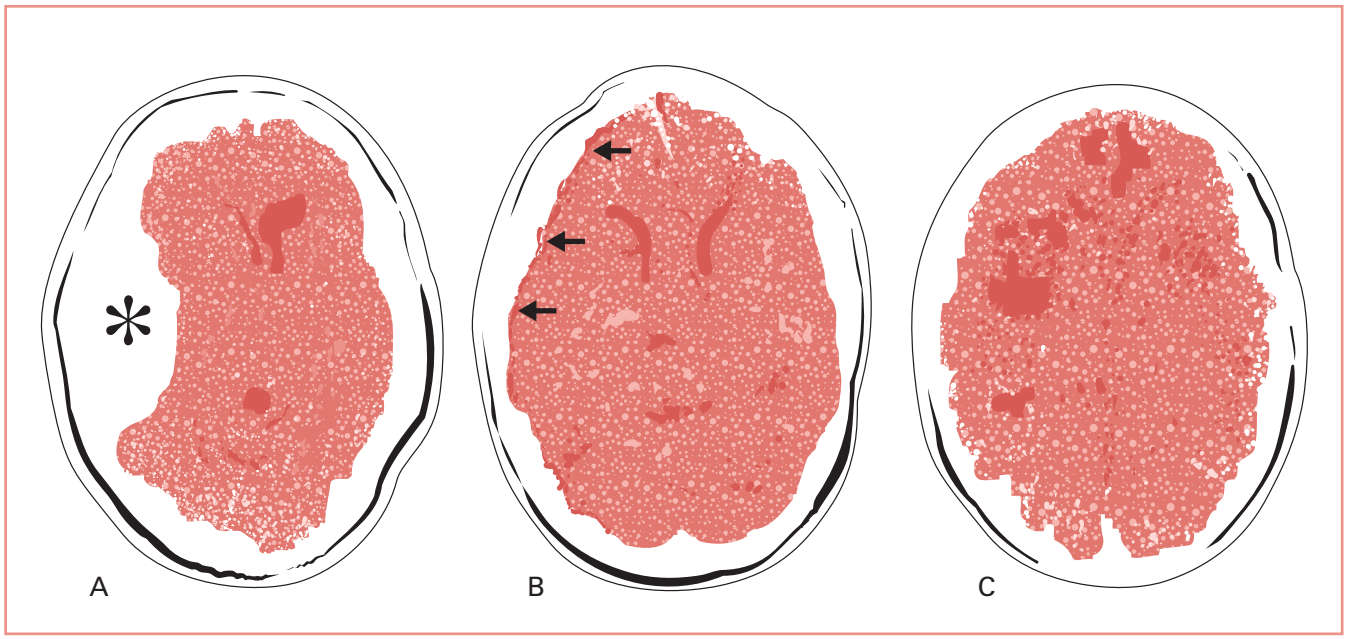

Figure 78.2. A, Epidural hematoma (asterisk). Note convex borders and midline shift. B, Subdural hematoma (arrows). Note the crescent shape. C, Diffuse axonal injury. Note the ground-glass appearance and tightly compressed ventricles.

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Evaluation

History

History is obtained during the secondary survey or reassessment phase of evaluation. Prehospital health professionals or witnesses to the injury should be asked about details of the event and the child's status following the event (Box 78.2).

Physical Examination

Careful attention to the vital signs of the child with head injury is important. The presence of hypertension, bradycardia, and an irregular breathing pattern (ie, *Cushing triad*) is suggestive of a significant intracranial injury with associated increased ICP.

Box 78.2. What to Ask

Head Trauma

- What was the mechanism of injury (eg, motor vehicle crash, ejection from motor vehicle, fall, assault)?
- If a fall, what was the height of the fall?
- What was the type of impact surface?
- What was the shape of the object(s) striking the head?
- What was the child's immediate status after injury?
- What changes in status occurred before arrival at the hospital?
- Did the child lose consciousness? If so, for how long?
- Did the child vomit?
- Did the child have a seizure? If so, when did it occur in relation to the injury, and does the child have an underlying seizure disorder?

Secondary survey actions include palpation and inspection of the scalp for soft tissue swelling, step offs (ie, indentation of the skull), lacerations, and fullness of the fontanel. Facial bones should be tested for stability and deformities. Other clues to possible head trauma include the presence of a septal hematoma, draining blood or fluid from the nose or ears, dental injury, and malocclusion of the mandible. The tympanic membranes should be visualized for the presence of hemotympanum or cerebrospinal fluid otorrhea, which, along with postauricular ecchymosis (ie, Battle sign), periorbital ecchymosis (ie, raccoon eyes), or cranial nerve palsies, is suggestive of a basilar skull fracture. If possible, funduscopic examination should be performed to look for the presence of papilledema associated with increased ICP or retinal hemorrhages, which are indicative of nonaccidental trauma.

A comprehensive neurologic examination is the most important aspect of the secondary survey. This examination should include a mental status assessment, cranial nerve evaluation, and assessment of the presence and quality of deep tendon reflexes, muscle tone, muscle strength, sensation, and cerebellar function.

When describing mental status, imprecise terms such as "altered," "lethargic," and "obtunded" should be avoided. Several scoring systems are available for assessing the mental status of children who have sustained head trauma. Many are useful predictors of intracranial injury and are also useful in assessing level of consciousness in pediatric patients. The most universally accepted and widely used of these scales is the *Glasgow Coma Scale* (GCS). It is used routinely in children older than 5 years but can be modified for younger children. Like many other systems, the GCS measures responses to a variety of stimuli in 3 areas—eye opening, verbal, and motor. Scores should be tabulated when the child first presents to establish a baseline, after

which the scores can be used for reassessment on a regular basis until the patient has stabilized or returned to normal mental status. Use of these scores helps promote consistent and accurate communication among health professionals. Table 78.1 shows how to calculate the GCS and modified GCS. In some circumstances the calculation of a precise GCS can be cumbersome, especially in time-critical situations. Several rapid scoring systems have been developed and are currently under active study. One system, the AVPU, describes the type of stimulus required to provoke response in a patient as either alert, verbal, painful, or unresponsive. Recent literature has shown that either an alert or a verbal response strongly correlates with a GCS above 8.

Laboratory Tests

A complete blood cell count and serum electrolyte panel should be performed for all pediatric patients with significant head trauma. Bedside glucose monitoring should be performed in any child with a head injury with an altered level of consciousness. Toxicology evaluation may be indicated in the adolescent who appears to be intoxicated or has an altered level of consciousness. The infant or child with an intracranial hemorrhage should undergo screening coagulation studies (ie, prothrombin time, activated partial thromboplastin time) as well as a type and screen test or crossmatch, in case surgery is required.

Imaging Studies

In cases of acute pediatric blunt or penetrating trauma, a noncontrast CT of the head is currently the diagnostic study of choice. It is quite sensitive for the detection of acute hemorrhage and skull fracture. It can also provide additional information on the severity of injury, indicating increased ICP, cerebral edema, or pending herniation. Among the findings on CT that indicate severe brain injury are the shift of midline structures, effacement of the sulci, ventricular enlargement or compression, and loss of normal gray/white matter differentiation.

An emergent head CT is warranted for any child with altered mental status, a GCS below 14, penetrating trauma, or focal neurologic deficit. The question of which children with minor head trauma should undergo CT was evaluated in a study of 17,000 children from the Pediatric Emergency Care Applied Research Network (PECARN) database. In this study, a decision rule was retrospectively derived and then prospectively validated as a method to identify children at very low risk for intracranial injury. These criteria can be found in Box 78.3. If a child is otherwise healthy and meets these criteria, the risk of intracranial injury is extremely low and the child can be safely discharged from the ED or clinic with anticipatory guidance and return precautions. Neither CT nor a period of observation is required. It should be noted that this decision rule was validated as "rule out" only and meant to identify the child at very low risk. If a child does not meet all the criteria, it does not mean a CT scan is required.

With the speed and widespread availability of CT machines, radiographs of the skull have relatively little role in the acute evaluation of pediatric patients with head trauma. Currently, CT can be performed very quickly, often with little or no need for sedation. Although plain radiographs are sensitive for the detection of

Table 78.1. Pediatric Glasgow Coma Scale

	>1 Year		*< 1 Year*	*Score*
Eye Opening	Spontaneously		Spontaneously	4
	To verbal command		To shout	3
	To pain		To pain	2
	No response		No response	1
Motor Response	Obeys		Obeys	6
	Localized pain		Localized pain	5
	Flexion-withdrawal		Flexion-withdrawal	4
	Flexion-abnormal (decorticate rigidity)		Flexion-abnormal (decorticate rigidity)	3
	Extension (decerebrate rigidity)		Extension (decerebrate rigidity)	2
	No response		No response	1
	>5 Years	*2-5 Years*	*0-23 Months*	
Verbal Response	Orientated	Appropriate words/phrases	Smiles/coos appropriately	5
	Disorientated/confused	Inappropriate words	Cries and is consolable	4
	Inappropriate words	Persistent cries and screams	Persistent inappropriate crying and/or screaming	3
	Incomprehensible sounds	Grunts	Grunts, agitated, and restless	2
	No response	No response	No response	1
			Total Pediatric Glasgow Coma Score (3-15)	

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Box 78.3. Low-risk Criteria for Pediatric Intracranial Injury

Age <2 Years

- Normal mental status
- No scalp hematoma except frontal
- No loss of consciousness, or loss of consciousness for <5 seconds
- Non-severe injury mechanism
- No palpable skull fracture
- Acting normally according to parents

Age ≥2 Years

- Normal mental status
- No loss of consciousness
- No vomiting
- Non-severe injury mechanism
- No signs of basilar skull fracture
- No severe headache

skull fractures, they do not provide any information about associated intracranial injuries. Additionally, several studies have demonstrated that intracranial injuries occur in the absence of a skull fracture, particularly among young pediatric patients. Plain radiography is obtained only as part of the skeletal survey in cases of suspected nonaccidental trauma.

Magnetic resonance imaging has little role in the treatment of the patient with acute injury resulting from head trauma. Computed tomography is often more sensitive in detecting acute intracranial hemorrhages and is sufficient to guide most immediate patient care issues. Magnetic resonance imaging may be superior to CT for identifying DAI and subtle brain injuries. Generally, magnetic resonance imaging takes longer to complete and often requires sedation, and the scanners frequently are located away from the ED in an area in which the child cannot be monitored appropriately.

One important consideration with any trauma victim is the possibility of a cervical spine injury. Although cervical spine injuries are rare in children, the physician must maintain a high index of suspicion when presented with a child who has suffered significant head trauma, particularly from a high-energy mechanism such as an unrestrained motor vehicle crash. Careful evaluation and imaging of the cervical spine is required for all children with an altered level of consciousness; significant, painful, distracting injuries; an inability to communicate; focal neurologic deficits; or localized pain, swelling, or ecchymosis of the cervical spine. Younger children (<8 years) have a larger occiput-body ratio than older children and adults and consequently a higher fulcrum; thus, most cervical spine injuries in this age group tend to be at higher levels (ie, C1, C2, C3). Furthermore, as the result of increased flexibility and lack of ossification, children are at risk for ligamentous or direct cord injury in the absence of a bony injury. The physician should maintain a high index of suspicion with severely injured children, even if no bony injury is evident on radiographs or CT.

Management

Assessment and management occur simultaneously in the child with acute injury. A primary survey is initially performed with attention to circulation, airway, and breathing as well as cervical spine immobilization. Prompt neurosurgical consultation should be obtained for all children with significant head trauma to assess the need for surgical management and ICP monitoring. The primary management goal of significant acute head trauma is the prevention of secondary brain injury by maximizing oxygenation and ventilation, supporting circulation to maximize cerebral perfusion, decreasing elevated ICP, and decreasing cerebral metabolic demands.

Individuals with significant intracranial injuries often require intubation for airway protection. Those individuals with a GCS score of 8 or lower should undergo rapid sequence intubation to control the airway. These individuals should be premedicated with a sedative. Historically, etomidate was the sedative of choice because it is cardiovascular neutral with minimal effect on blood pressure and because most other sedatives can cause hypotension, thereby decreasing MAP and reducing CPP. One area of controversy involves the use of ketamine for sedation prior to intubation. Ketamine is well known to raise the MAP, which has a positive effect on CPP; however, it was historically thought to increase ICP, thus making it less ideal. Recent literature, mostly in adults, has called into question the effect of ketamine on ICP. Currently, no clinical data exist to recommend or not recommend ketamine as an indication agent for intubation in a severely injured pediatric patient with head trauma. Historically, lidocaine was thought to potentially blunt the transient increase in ICP often associated with direct laryngoscopy and orotracheal intubation. Given no difference in outcomes and questionable benefit recent recommendations based on adult literature no longer recommend routine administration of lidocaine before rapid sequence intubation in patients with head trauma. Although there are no published trials involving children, short-acting opioids such as fentanyl (1 mcg/kg) may be considered prior to induction to blunt response to direct laryngoscopy and rapid sequence intubation. When intubation is indicated, steps should be taken to minimize desaturations, because several studies have demonstrated worse outcomes with hypoxia in children with severe traumatic brain injury.

Historically, moderate hyperventilation was advocated to reduce ICP. Hyperventilation reduces partial pressure of carbon dioxide, arterial, resulting in cerebral vasoconstriction and decreased cerebral blood flow, thereby reducing ICP. This has been shown to have the unwanted effect of disrupting cerebral metabolism and possibly exacerbating ischemic injury. Currently, normal ventilation is recommended, with the goal of maintaining partial pressure of carbon dioxide, arterial, no lower than 34 mm Hg. Moderate hyperventilation may have a role in the transient management of serious or acute life-threatening elevations in ICP (ie, acute herniation) as a temporizing measure until more definitive care (eg, neurosurgical decompression) can be performed.

Circulation and MAP should be aggressively supported with fluids to prevent hypoperfusion to the brain. Hypovolemia or

hypotension should never be assumed to result from head trauma alone. The child should be examined carefully for evidence of additional injury. Central venous pressure monitoring may be useful in addressing volume status; however, recent literature has suggested that point-of-care bedside ultrasonography of the size of the inferior vena cava and its respiratory variation may provide a reliable estimate of the patient's intravascular volume status. Vasoactive medications may be necessary to maintain MAP in patients with euvolemia. Morbidity has been shown to significantly increase with subsequent episodes of hypotension.

Elevations in ICP may impede cerebral blood flow and exacerbate ischemic injury. Administration of hypertonic solutions is indicated in the management of increased ICP, particularly with signs of herniation. In the most recent guidelines, hypertonic (3%) saline is the first-line agent (as opposed to mannitol). If hypertonic saline is not readily available or the patient does not have the appropriate access for its administration, however, mannitol can be used as a temporizing measure. It is important to note that the use of mannitol and other diuretics is contraindicated in patients with borderline blood pressures because these agents can cause hypotension, which can in turn decrease the MAP, thereby worsening cerebral perfusion. Additionally, elevation of the head of the bed to 30° to promote venous drainage is also used to reduce ICP. Paralytic agents, sedatives, and analgesics may be necessary to prevent agitation, which also results in increased ICP and increases cerebral metabolic demands. Painful procedures (eg, suctioning) should be preceded by administration of adequate premedication with sedatives and analgesics. The use of intraventricular pressure catheters is often necessary to allow for close monitoring of ICP. Additionally, these can be used to drain cerebrospinal fluid to help decrease elevated ICP.

Hyperthermia and seizure activity should be managed aggressively, because they increase cerebral metabolic demands. Hyperthermia should be managed with antipyretic agents and active cooling measures. Conflicting evidence exists on controlled hypothermia in children with severe brain injuries. The most recent meta-analysis did not show a benefit for therapeutic hypothermia in children; however, this remains an area of active study. Anticonvulsant prophylaxis should also be considered in the child with severe brain injury, especially within the first 7 days. It is important to remember that the ability to detect clinical seizure activity is lost if the child is paralyzed.

Serum electrolyte levels should be followed closely, and any alterations should be minimized. The patient with head injury should be monitored closely for the development of diabetes insipidus or syndrome of inappropriate antidiuretic hormone.

Often, the child with a large epidural and subdural hematoma requires surgical evacuation. The individual with a depressed skull fracture often requires surgery to lift the depressed fragment away from the underlying brain. The child with significant penetrating head trauma warrants antibiotic and antiepileptic prophylaxis and may need angiography to assess for vascular injury. In all cases, tetanus status should be updated if necessary.

As previously discussed, the child with no high-risk criteria as outlined by the PECARN guidelines can be safely discharged without a period of observation or neuroimaging. However, the child with minor head injury (GCS score, 14–15) who does not strictly meet the PECARN criteria warrants either a period of observation or CT evaluation. Signs of a basilar skull fracture and altered mental status are considered high-risk features, and the affected patient should undergo prompt CT of the head. Mechanism of injury, a scalp hematoma in children younger than 2 years, and severe headache and vomiting in children age 2 years and older are less specific for intracranial bleeding or skull fracture. Therefore, in these patients a period of observation, including a cautious challenge orally of food or liquid, is a reasonable strategy to avoid the radiation risk of CT. An algorithm of this approach is shown in Figure 78.3. The optimal time of observation is unknown; however, in most EDs a 6-hour observation period is considered appropriate. If during the observation period the child deteriorates clinically or does not return to baseline, CT of the head should be performed. The physician should be wary of discharging a child whose condition has not improved to baseline after minor injury or who has persistent emesis, even if CT is normal.

More moderate head injuries (initial GCS score, 9–12) necessitate a longer period of evaluation, likely in a monitored setting along with neurosurgical consultation. Severe head injuries (GCS score < 8) require aggressive stabilization in the ED with the measures described previously and admission to a pediatric intensive care unit.

The child who has sustained a concussion warrants close observation and reevaluation before resuming sports activities, because mounting evidence exists that multiple, sequential concussions can have long-term debilitating effects. The American Academy of Neurology has guidelines for evaluation and return-to-play parameters. These recommendations include an evaluation by a health professional familiar with concussion and the use of sideline assessment tools to rapidly evaluate the athlete for removal from play. Before returning to play, the athlete should have complete physical and cognitive rest until the athlete is symptom-free. Additionally, the neurologic examination and imaging (if performed) should be normal. Some programs use neuropsychiatric testing to evaluate for subtle deficits in the evaluation of return to play. Generally, the emergency physician should stress to the athlete being evaluated the serious nature of a concussion and not clear the athlete to play from the ED; rather, the patient should be referred through the appropriate protocols of the team.

Prognosis

Age is the most important prognostic factor in outcome. Younger children tend to do better than older children. It remains difficult to predict the outcome of any individual patient. Scalp lacerations, most skull fractures, and concussion are low-risk injuries. Intracranial hemorrhage, specific skull fractures, head injury secondary to nonaccidental trauma, and trauma accompanied by diffuse cerebral edema are high-risk injuries. If untreated, severe head injury may result in death from herniation.

Other complications from severe head trauma are posttraumatic seizures, requiring lifelong treatment with anticonvulsants;

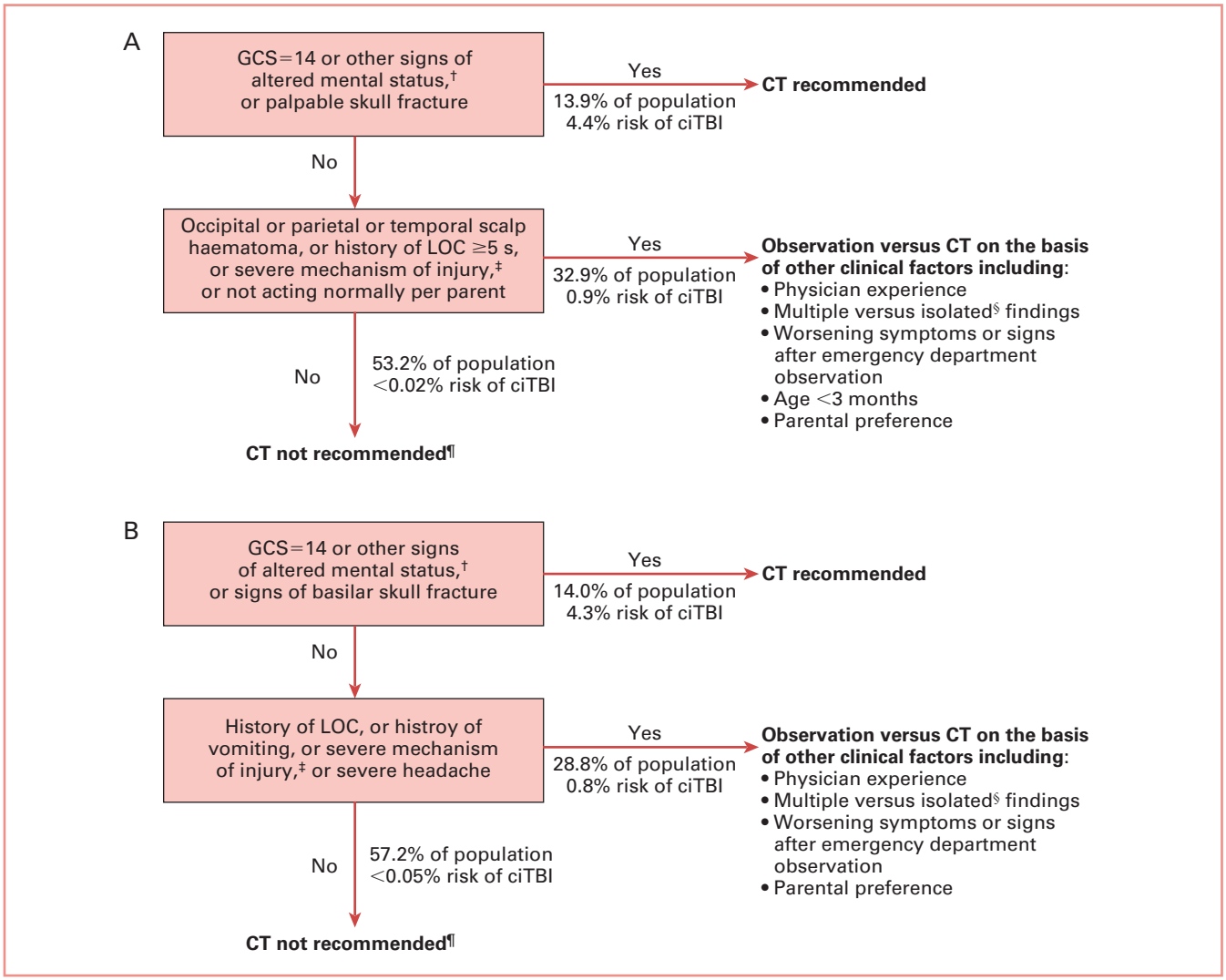

Figure 78.3. Suggested algorithm for computed tomography in children younger than 2 years (A) and for those age 2 years and older (B) with GCS scores of 14 to 15 after head trauma.*

Abbreviations: ciTBI, clinically-important traumatic brain injury; CT, computed tomography; GCS, Glasgow Coma Scale score; LOC, loss of consciousness; s, seconds.

* Data are from the combined derivation and validation populations.

† Other signs of altered mental status: agitation, somnolence, repetitive questioning, or slow response to verbal communication.

‡ Severe mechanism of injury: motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a high-impact object; falls of more than 0.9 m (3 ft) (or more than 1.5 m [5 ft] for panel B); or head struck by a high-impact object.

§ Patients with certain isolated findings (ie, with no other findings suggestive of traumatic brain injury), such as isolated LOC, isolated headache, isolated vomiting, and certain types of isolated scalp hematomas in infants older than 3 months, have a risk of ciTBI substantially lower than 1%.

¶ Risk of ciTBI exceedingly low, generally lower than risk of CT-induced malignancies. Therefore, CT scans are not indicated for most patients in this group.

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hydrocephalus, necessitating placement of a ventriculoperitoneal shunt catheter; and persistent vegetative or severely impaired mental state. Penetrating head injuries can result in infections (eg, meningitis, abscess) and vascular injuries (eg, aneurysm, arteriovenous malformations). Sequelae such as postconcussion syndrome may result from less severe head trauma. Some of the characteristics of this syndrome include dizziness, headache, irritability, memory deficits, impaired behavior, and impaired cognitive development. These may persist for months after the head injury and sometimes are permanent. The child with postconcussion syndrome may warrant formal neurobehavioral testing.

Prevention

Despite advancing medical knowledge and excellent critical care available to children with head trauma, little can be done to reduce the severity of primary brain injury after it has occurred. Therefore, pediatric health professionals should make every attempt to educate patients and families about prevention strategies. Some of the most

successful prevention strategies involve the required use of restraint devices (eg, seat belts) and proper safety gear (eg, bicycle helmets). Anticipatory guidance and home safety recommendations provided to parents and caregivers are also worthwhile. Finally, communities can contribute to injury prevention by providing playground resurfacing, reducing the height of playground equipment, and changing traffic laws. It is only through a combination of these prevention strategies that morbidity and mortality of pediatric head trauma will be meaningfully reduced.

CASE RESOLUTION

The young child has a significant mechanism of injury, brief LOC, and a depressed, altered mental status. Initial physical findings prompt suspicion of a depressed skull fracture and overlying soft tissue injury. Appropriate diagnostic tools after evaluation of circulation, airway, and breathing are cranial CT followed by admission for observation, monitoring, and serial neurologic examination. Surgical repair of the skull fracture may be necessary.

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CHAPTER 79

Increased Intracranial Pressure

Hanalise V. Huff, MD, MPH, and Kenneth R. Huff, MD

CASE STUDY

A 7-year-old boy has a 2-week history of recurrent vomiting. No fever, abdominal pain, or diarrhea has accompanied the vomiting; the vomiting has no particular relationship to meals; and the boy's appetite has decreased only slightly. The vomiting has gradually increased in frequency and is occurring every night. The day before this visit there were 4 episodes. The boy's parents have noticed that their son is generally less active; he spends more time playing on the floor of his room and does not want to ride his bicycle or play with neighborhood friends. Some unsteadiness in the boy's gait has manifested in the past few days. His parents attribute this to weakness from the vomiting.

The child's vital signs are normal except for a blood pressure of 130/80 mm Hg. Although the boy is somewhat pale and uncomfortable, he does not appear to be in acute distress. His abdominal examination is unremarkable. His speech is grammatically correct but sparse and hesitant, and he seems inattentive. On lateral and upward gaze the boy has coarse nystagmus, and upward gaze is somewhat limited. Dysconjugate left gaze is apparent, with slight failure of left eye abduction. The left eye does not blink as much as the right eye. Fundal examination discloses elevated discs with indistinct margins. No upper extremity weakness is evident. The right foot is slightly weaker than the left, ankle tone is bilaterally increased, and 3 to 4 beats of clonus on the right and bilateral positive Babinski reflexes are present. Some tremor occurs in both arms with finger-to-nose testing. The boy walks with shuffling, small steps; his gait has a slight lurching character; and he veers to the right.

Questions

1. What clinical situations are associated with increased intracranial pressure?
2. What is the pathophysiological process leading to increased intracranial pressure?
3. What studies are used to evaluate the child with increased intracranial pressure?
4. What measures are used to treat the child with increased intracranial pressure?

The signs and symptoms of increased intracranial pressure (ICP) often signal a serious, potentially brain damaging intracranial process that may require surgical or intensive care intervention depending on the underlying cause. Recognizing signs and symptoms early often results in a determination of the underlying cause, after which management can resolve the secondarily increased ICP problem. Increased ICP can also be a critical care issue by itself even if the specific etiologic diagnosis is indeterminate. A growing number of effective medical and surgical treatments for increased ICP are available. It is critical to have an understanding about when to initiate them because they can be lifesaving.

Epidemiology

A wide variety of clinical situations, including both acute and subacute processes that occur at all ages, in both sexes, and among all ethnic groups, are commonly responsible for increased ICP. Only a few can be mentioned herein. Traumatic brain injury (TBI) is a leading cause of increased ICP. Fifty-two percent of infants with TBI may be victims of nonaccidental trauma; older children may be stricken pedestrians or bicycle riders, occupants of crashed motor vehicles, or victims of falls or sports injuries; and children of any age may suffer gunshot wounding. Traumatic brain injury is the leading source of trauma mortality and morbidity in children, most often as the result of brain-damaging increases in ICP.

Brain tumors are the most common solid neoplasms in children and frequently result in subacutely increased ICP by direct mass effect or blockage of cerebrospinal fluid (CSF) flow. Diagnosis may sometimes be suggested by neurocutaneous signs or other evidence of tumor suppressor gene mutation. Ischemic brain damage resulting from a difficult delivery at birth, a near drowning incident, or a major intracranial arterial or venous vessel thrombosis is also a significant etiologic contributor to increased ICP. Other causes of brain swelling, such as lead intoxication and liver failure in Reye syndrome, have become less common etiologies.

Idiopathic intracranial hypertension (IIHP, also called benign intracranial hypertension or pseudotumor cerebri), which has an overall prevalence of 1 to 2 per 100,000 but is 20 times higher in adolescent girls with obesity, may ultimately be found as the cause for the increased ICP. It often occurs spontaneously but may also follow the use of high doses of vitamin A, growth hormone, or tetracycline, or it may occur after withdrawal of steroid therapy. Similar physiology is seen with thrombosis of a venous sinus caused by a clotting diathesis or complicated otitis media or mastoiditis.

Clinical Presentation

The child with increased ICP may present with a history of recurrent vomiting, lethargy, and new headaches of increasing frequency or severity (ie, crescendo headaches) or that awaken the child from sleep. The physician must be acutely aware of the clinical situation. A prior history of trauma, ischemia, meningitis, hypertension, or vasculitis; presence of a CSF shunt; or a concomitant history of intoxication or metabolic aberration (ie, carbon monoxide, hyperammonemia, or diabetic ketoacidosis) may also be suspicious for increased ICP in the child with compatible examination findings. Neonates with intraventricular hemorrhage or myelomeningocele or other major central nervous system malformations are prone to hydrocephalus. Children with cyanotic congenital heart disease are prone to cerebral abscesses, and children with sickle cell disease can present with stroke or hemorrhage, resulting in increased ICP. In endemic areas of the world, cerebral malaria and intraventricular cysticercosis are frequent causes of increased ICP. The pertinent physical findings may include elevated optic disc, failure of upward gaze, hypertonicity of the extremities, and either depressed alertness or inattention or severely altered mental status. More localized findings on neurologic examination may also point to a lesion indicative of a space-occupying intracranial mass, which could contribute to increased ICP (Box 79.1).

Pathophysiology

The problem of increased ICP can be understood in terms of the Monro-Kellie doctrine, which applies to the rigid cranial compartment and pressure-volume relationships of the contents. This doctrine is conceptually useful even though not always quantitatively predictive because of the variable compliance of the child's skull and dural membranes, particularly in the first 2 years after birth before most of the cranial sutures are fused. The skull and dura mater form a relatively rigid compartment; any increase in 1 of the 3 intracranial volume components—brain parenchyma, CSF, and blood—must occur at the expense of 1 or both of the other 2. Decreased volume results in increased pressure in an inverse relationship; the rise becomes much steeper, however, when initial compliance factors are overwhelmed. Irreversible damage to brain tissue occurs primarily as a result of pressure of the other components overtaking the arterial blood pressure and not allowing adequate tissue perfusion. In younger children, nonfused sutures allow more compliance if volume increases are relatively slow, but this factor is less true for acute volume increases. Additionally, pressure gradients exist across compartments or sites of CSF flow obstruction, or even around lesions within brain parenchyma, which results in focal findings in addition to those caused by global ICP or perfusion changes.

Box 79.1. Diagnosis of Increased Intracranial Pressure

- Loss of appetite, nausea, vomiting, headache, or lethargy
- Inattention, decreased ability to arouse
- Full fontanelle, increased head circumference
- Papilledema, upward gaze paresis
- Increased tone, positive Babinski reflex
- Focal signs and history compatible with an intracranial mass
- Mass lesion, cerebral edema, occluded major vessel, or enlarged ventricles on an imaging study
- Elevated cerebrospinal fluid pressure in the lumbar intrathecal or intracranial space as measured using a manometer

Changes in any of the 3 components comprising the intracranial volume may result in increased ICP in several ways. First, the brain parenchyma component may be directly increased by mass lesions, such as neoplasms, abscesses, or hemorrhages. Vasogenic edema may increase the brain parenchyma volume because of vascular leakage due to cytokines. Brain edema may also result from cytotoxic damage, cell death, and necrosis, producing increased interstitial oncotic pressure from released proteins and ions, and cellular inflammatory and repair processes. The immediate cause may be mediated by cellular insults, including hypoxemia; intermediary metabolic toxins, including neuronal excitotoxins; and depletion of energy substrates that are consequential to major vessel occlusion, contusional trauma or traumatic diffuse axonal injury, anoxia from cardiac arrest, hypertensive encephalopathy, encephalitic infection, or external metabolic poisoning. Edema with head trauma is known to be worse in children than in adults and may be a combination of vasogenic and cytotoxic edema and may be related to neurogenic inflammatory release of substance P and calcitonin gene-related peptide at the molecular level close to vessels.

Second, the pressure of the CSF volume component (ventricles or subarachnoid spaces) may increase in the setting of hydrocephalus. Hydrocephalus can result in 2 ways: from a discrepancy in the rate of formation of CSF relative to absorption and from an obstruction between the point of formation in the lateral ventricles and the sites of absorption at the arachnoid granulations. An obstruction can occur with a congenital malformation; a parenchymal or intraventricular mass, such as a cyst or neoplasm; CSF inflammatory cells from meningitis, ventriculitis, or hemorrhage; subarachnoid protein or debris; displaced brain parenchyma from mass effect; or overgrowth of dural tissue. The small passageways connecting the ventricular system, the foramen of Monro, and the aqueduct of Sylvius; the exits of the ventricular system, the foramen of Magendie, and the foramen of Luschka; and the cisterns surrounding the brain stem are particularly vulnerable points of obstruction. Another type of brain edema, interstitial edema, is characterized by periventricular transudation of CSF into the adjacent white matter and generally occurs in the patient with acute or subacute hydrocephalus.

Third, ICP may rise because the intravascular volume component may increase. One process that leads to this increase is venous outflow obstruction, such as with a dural sinus thrombosis. Many patients initially diagnosed as having IIHP are subsequently found to have a diagnosis of transverse sinus stenosis or thrombosis. Other processes that raise jugular venous pressure may also increase ICP. Additionally, the intracranial arterial vascular volume is affected

by partial pressure of carbon dioxide. It not only increases with hypercapnia and inadequate ventilation but also decreases with hypocapnia, which occurs with compensatory central neurogenic hyperventilation or iatrogenic reduction of ICP by mechanical hyperventilation.

Because the physiology is dynamic, it has proven useful to quantitate ICP for management purposes. Intracranial pressure is often measured as centimeters of water (cm H_2O), whereas blood pressure is noted as millimeters of mercury (mm Hg). Normal ICP levels are somewhat lower in the neonatal and infantile period, at approximately 6 cm H_2O (5 mm Hg), but in adolescents, pressures above 25 cm H_2O (18 mm Hg) are abnormal and may produce symptoms. Although it is possible to have normal cognitive function at an ICP of 52 cm H_2O (40 mm Hg), this assumes an adequate perfusion pressure. Perfusion pressure is the mean arterial pressure (MAP) less the ICP. The ICP becomes clinically significant when the perfusion pressure is compromised, which may occur when the ICP is 78 cm H_2O (60 mm Hg) below the MAP, which might translate to an ICP as low as 20 mm Hg if the MAP is 80 mm Hg. It can become dangerous when the ICP is only 52 cm H_2O (40 mm Hg) below the MAP, which translates to an ICP of 40 mm Hg if the MAP is 80 mm Hg. Decreased perfusion produces swollen, damaged tissue, which increases the brain parenchymal compartment volume and further exacerbates the pressure-volume problem in a cascading fashion. Total loss of brain perfusion occurs when the rise in ICP overtakes and becomes equal to the MAP.

As ICP increases, brain perfusion pressure may be maintained transiently by a spontaneous increase in MAP, a response referred to as the *Cushing response* (ie, hypertension along with bradycardia and bradypnea). Although the relationship may not be universally reliable, when it is present with other suggestive clinical circumstances, the rise in systemic pressure can be a useful clinical sign of increased ICP. Normally, changes in arterial cerebrovascular resistance meet changes in perfusion pressure to maintain constant cerebral blood flow, a process called *autoregulation*. This process is frequently compromised after head trauma or asphyxia, however, and is shifted with chronic hypertension.

Acute or subacute changes in pressure within an intracranial compartment may produce a pressure gradient across compartments that may precipitate brain herniation syndrome (Figure 79.1). An ominous heralding sign of transtentorial herniation of the uncus of the temporal lobe is loss of the pupillary light reflex caused by entrapment of cranial nerve III. This herniation often results in irreversible brain stem damage as well as infarcts and additional secondary edema, which can end with brain death. Focally increased posterior fossa pressure may result in a pressure cone downward through the foramen magnum, compressing medullary centers, sequentially extinguishing cranial nerve functions, producing decerebrate posturing, and finally causing apnea and brain death. A marginally compensated system could be decompensated by an ill-advised lumbar puncture when the spinal compartment pressure is acutely decreased, thereby increasing the pressure gradient across the foramen magnum and producing herniation.

Differential Diagnosis

Complicated migraine, seizures, and metabolic derangements are common problems that sometimes have a clinical presentation similar to increased ICP because they may present with headache and altered mental status. A characteristic prodrome or the "pounding"

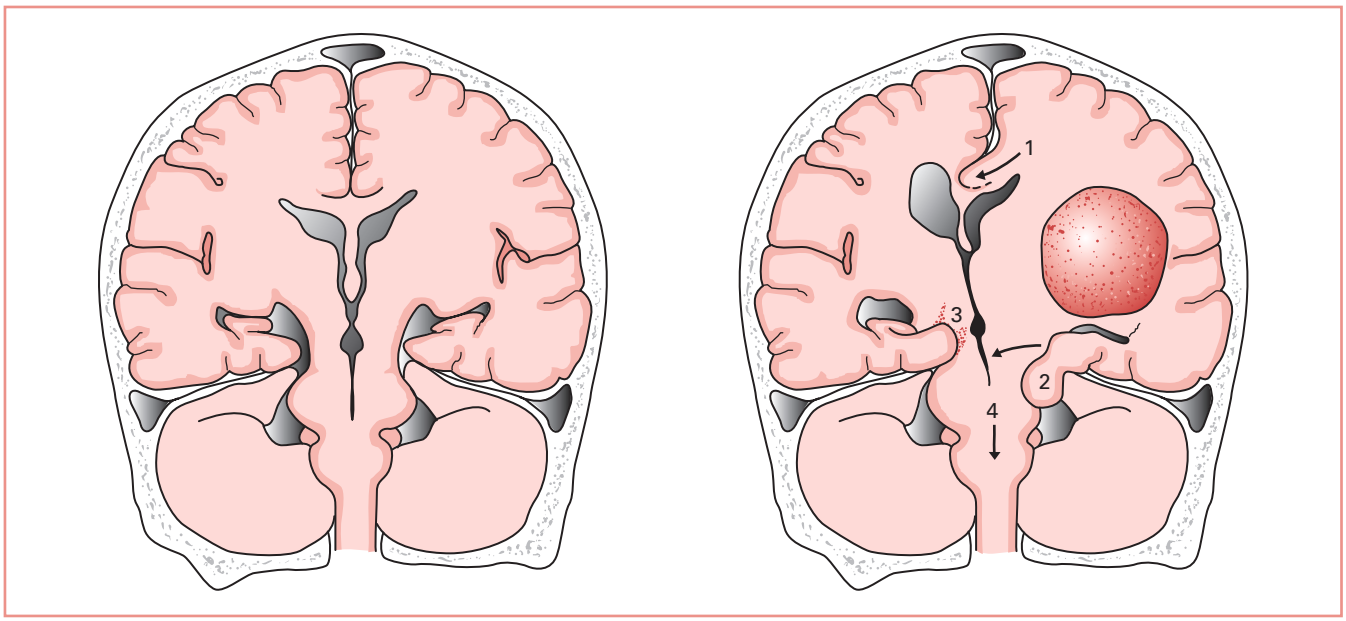

Figure 79.1. Left, Illustration of a normal brain. Right, Illustration of the anatomy of several potential herniation syndromes caused by intracranial compartment pressure gradients related to a mass in a cerebral hemisphere. 1, Transfalcine herniation. 2, Uncal herniation. 3, Contralateral tentorial-midbrain damage. 4, Central herniation and foramen magnum pressure cone. These syndromes often result in further brain ischemia and additional increases in intracranial pressure.

nature of the pain may help separate migraine from increased ICP. At the initial headache presentation or when only a short headache history is present, the complicated migraine diagnosis may be one of exclusion. If the child displays focal neurologic signs with some of the general symptoms of increased ICP, an imaging study to rule out a space-occupying lesion and confirm the safety of a lumbar puncture as well as a subsequent measurement of normal pressure by lumbar puncture manometry may be necessary to support the diagnosis of complicated migraine rather than increased ICP.

In the child who is only partially responsive, the task of distinguishing a seizing or postictal state from a condition that may be producing increased ICP is sometimes difficult. Findings suggestive of a seizure include rhythmic, clonic movements or sudden myoclonic jerks; rapid or variable changes of tone or posturing that are different from the decerebrate posturing that may accompany a process producing increased ICP; abrupt, fluctuating changes of autonomic function (eg, heart rate, blood pressure, pupillary size); saliva production without swallowing; and a history of prior seizures. Sometimes, however, only direct electroencephalography (EEG) monitoring with ICP monitoring can distinguish ongoing electrographic "subclinical" seizure activity from increased ICP as the cause of the change in level of responsiveness.

In some instances, diffuse brain dysfunction from a toxic or metabolic etiology mimics increased ICP. Such toxic or metabolic causes include medication toxicity, electrolyte or blood chemistry imbalance, and systemic infection. With toxic or metabolic disorders, inattention is often accompanied by an acute confusional state with disorientation, incoherence, and sometimes agitation. In contrast, with subacutely increased ICP, inattention frequently is accompanied by slowness of thought, perseveration, decreased mental activity, and impaired gait.

Evaluation

History

A thorough neurologic history should be obtained (Box 79.2). Headache, nausea and vomiting, drowsiness, personality change, declining school performance, and changes in visual acuity and obscurations are important historical factors. The headache history may be one of crescendoing in frequency or intensity, consistent localization, and only a few days' or weeks' duration. The headache may awaken the patient from sleep or be worsened by cough, micturition, defecation, or other Valsalva-like maneuvers. A "thunderclap" headache may be indicative of an intracranial hemorrhage. Rapid progression of symptoms generally motivates concern.

Box 79.2. What to Ask

Increased Intracranial Pressure

- How long has the child been vomiting, and when does the vomiting occur?
- Do headaches awaken the child?
- Does the child have weakness or change in gait?
- Does the child have a recent history of trauma?
- Has there been a progressive decline in activity level or loss of developmental skills?

Physical Examination

Vital signs and head circumference should be noted. Neck stiffness is an important sign of either meningeal irritation or cervical trauma. A careful neurologic examination is warranted whenever increased ICP is suspected. Particular attention should be paid to the components of the mental status and level of responsiveness and alertness of patients. The presence of papilledema and the cranial nerve functions, including visual fields, should be assessed. Papilledema may not appear for a few days after ICP is increased. Retinal hemorrhages in an infant may be suspicious for nonaccidental trauma. Cranial nerve VI is particularly susceptible to increased ICP, and an abnormality may be falsely localizing. Impaired upward gaze and lid retraction may be present. The patient may tilt the head to compensate for dysconjugate gaze. Specific muscle tone and strength as well as gait characteristics and ataxia should be evaluated in the child who cannot cooperate. In the comatose child, posturing responses to stimulation and the breathing pattern should be noted to help ascertain brain stem localization of a lesion. In a comatose child, findings should be reassessed at frequent intervals until stable to follow a potentially rapidly progressing devastating process, such as impending tentorial or brain stem herniation, which would necessitate immediate surgical intervention.

A useful quick-assessment instrument for initial, rapid evaluation and subsequent monitoring is the pediatric *Glasgow Coma Scale* (Table 79.1). These scales are a useful shorthand description for emergent triage purposes and perhaps for acute ventriculostomy decisions in trauma cases but are not sufficient for all clinical decisions related to patients with increased ICP.

The newborn or infant may display a unique collection of signs—enlarged head circumference; bulging, raised fontanelle; frontal bone bossing with prominent venous distention; irritability, *setting sun sign* (ie, inability to elevate the eyes and lid retraction resulting from midbrain tectal pressure); hypertonicity; and hyperreflexia—that may be secondary to increased ICP resulting from hydrocephalus. Papilledema is generally not present, perhaps related to greater compliance of the newborn and infant skull.

Chronic hydrocephalus as a cause of increased ICP may result in optic atrophy, depressed hypothalamic functions, spastic lower limbs, incontinence, and learning problems.

Laboratory Tests

If mental status changes are suggestive of a toxic or metabolic aberration, appropriate laboratory screening should be performed, including complete blood count, glucose level, electrolyte level, toxicology screening, liver function tests, arterial blood gasses, and kidney function tests. If signs of meningeal irritation or infection are also present without lateralized signs of altered tone or strength, evidencing an intercompartmental pressure gradient, a CSF examination

should be done. Otherwise, if the patient is at risk for herniation after lumbar puncture, a preceding brain imaging study is necessary. If the imaging study suggests that performing a lumbar tap carries a risk, CSF analysis and pressure measurements can be done based on ventriculostomy instead. For the patient with clinical signs of increased ICP and no focal clinical or imaging signs of a mass, a lumbar puncture with opening pressure measurement is also necessary for the diagnosis of IIHP.

Imaging Studies

Computed tomography (CT) should be performed whenever a child's signs and symptoms indicate the possibility of increased ICP and should be performed even in the setting of symptoms without signs in a child younger than 6 years. Patients with severe head trauma frequently have a particularly dynamic pathophysiology, and an additional early CT scan after a few hours may be indicated to assess for increasing hemorrhage, mass effect, or ventricular size along with ICP monitoring. Magnetic resonance imaging may be necessary to detect ischemia early. Intravenous (IV) contrast should be given if a source of disruption in the blood-brain barrier (eg, infection, inflammation, neoplasia) is suspected. Magnetic resonance venography can be obtained if a possibility exists of a venous sinus thrombosis. Computed tomography angiography or traditional intraluminal angiography with the option of intervention to prevent rebleeding may be the best studies in the patient with intracranial hemorrhage of unknown source.

Management

If IIHP is diagnosed, the pressure can be monitored with lumbar punctures until it is stable. Visual fields can be monitored using optical coherence tomography to assess the degree of retinal damage. Monitoring should occur at regular intervals until full recovery. Increased ICP may respond to diuretic agents, such as acetazolamide at high dose (20 mg/kg/day) or furosemide, as well as the removal of CSF during the lumbar puncture as a temporizing measure. A weight loss program is quite important if obesity is present. The primary danger in this condition is eventual blindness caused by pressure at the optic nerve head. If medical therapy is not successful, lumbar or ventricular peritoneal shunt placement or optic nerve sheath fenestration can be done surgically. The risk of severe vision loss is 6% to 14%.

The child with encephalopathy whose ICP is markedly elevated or likely to rise rapidly requires treatment in an intensive care unit. When diagnostic imaging studies reveal an etiology for the increased ICP, such as a rapidly enlarging epidural hematoma, immediate neurosurgical craniotomy may be necessary. Other focal space-occupying lesions noted on imaging studies may not require immediate craniotomy, depending on size and position of the lesion as well as the distortion of normal brain tissue and potential for imminent loss of perfusion; neoplastic lesions may require diagnostic biopsy or excisional biopsy within a few days if surgically accessible. Mineralocorticoids (eg, dexamethasone 0.25–0.5 mg/kg every 6 hours) are useful in situations in which the

Table 79.1. Pediatric Glasgow Coma Scale

	>1 Year		*< 1 Year*	*Score*
Eye Opening	Spontaneously		Spontaneously	4
	To verbal command		To shout	3
	To pain		To pain	2
	No response		No response	1
Motor Response	Obeys		Obeys	6
	Localized pain		Localized pain	5
	Flexion-withdrawal		Flexion-withdrawal	4
	Flexion-abnormal (decorticate rigidity)		Flexion-abnormal (decorticate rigidity)	3
	Extension (decerebrate rigidity)		Extension (decerebrate rigidity)	2
	No response		No response	1
	>5 Years	*2-5 Years*	*0-23 Months*	
Verbal Response	Orientated	Appropriate words/phrases	Smiles/coos appropriately	5
	Disorientated/confused	Inappropriate words	Cries and is consolable	4
	Inappropriate words	Persistent cries and screams	Persistent inappropriate crying and/or screaming	3
	Incomprehensible sounds	Grunts	Grunts, agitated, and restless	2
	No response	No response	No response	1
			Total Pediatric Glasgow Coma Score (3-15)	

Reprinted with permission from Singh AP. Glasgow Coma Scale and Pediatric Glasgow Coma Scale. https://boneandspine.com/pediatric-glasgow-coma-scale/.

pressure is produced by a component of vasogenic edema, such as that surrounding neoplasms. Measures should also be used to help prevent a stress ulcer. Hypotonic IV fluids should be avoided, and serum and urine osmolality should be monitored for the syndrome of inappropriate antidiuretic hormone secretion. Hypoglycemia and hyperglycemia should be avoided as well. If the patient is in acute danger for herniation resulting from a pressure gradient produced by CSF flow blockage, a temporary ventriculostomy may be indicated to relieve the CSF pressure. If an infectious process is suspected, including focal lesions, abscess, cerebritis, or encephalitis, antibiotics or antiviral agents are indicated. After directed specific treatment of the underlying lesion, the increased ICP may resolve spontaneously. If hydrocephalus resulting from obstruction of CSF flow persists after initial therapy is completed, ventriculoperitoneal shunting of CSF may be necessary. Endoscopic third ventriculostomy avoids the long-term complications of obstruction and infection associated with ventriculoperitoneal shunt hardware but is less often successful in relieving the pressure in younger children than older ones.

In the patient with no mass or space-occupying lesion requiring surgical removal, interventional therapies are directed toward maintaining perfusion of recovering brain tissue. In the patient with head injury, a *Glasgow Coma Scale* score of 8 or less can be used as a guideline for ICP monitoring. Intracranial pressure can be monitored on an ongoing basis with commonly used neurosurgically placed devices, including the fiberoptic microtransducer and intraventricular catheter or ventriculostomy. The fiberoptic microtransducer can measure pressure in brain parenchyma as well as in fluid-filled spaces. A distinct advantage of the intraventricular catheter is in allowing for therapeutic CSF drainage to relieve pressure, although it may be difficult to place if the ventricles are small or shifted; additionally, this device carries a slight risk of hemorrhage or infection, increasing to a plateau at day 4 of 1% to 2% per day. Intracranial hypertension frequently peaks at 1 to 4 days after severe trauma. Intracranial pressure monitoring with devices and therapy based on the aforementioned measurements, however, has not been helpful in most patients with severe ischemic damage, infection, or poisoning. This finding may be because of the widespread nature of the insult and brain involvement so that little normally responding tissue remains in which perfusion could be maintained.

The child with a decreased or fluctuating level of responsiveness may require EEG monitoring of cerebral electrical activity. Seizures may occur even in the presence of increased ICP. Anticonvulsant therapy is indicated if evidence of clinical or electrographic seizures is present. Additionally, the EEG may be used to monitor barbiturate- or benzodiazepine-induced coma, which is used in the setting of severely increased ICP.

Respiratory physiology and ventilation are important for the child with increased ICP, because hypoxia and hypercapnia can contribute to vasodilation and increased pressure. Rapid sequence intubation and avoidance of ketamine and succinylcholine help minimize elevations of ICP. Transmission of elevated intrathoracic pressure to intracranial vessels can be avoided by sedation and decreasing the inspiratory phase of the ventilator and avoiding high positive pressure and end-expiratory pressure. If acute reduction of pressure is necessary, hyperventilation to reduce the intracranial arterial blood volume is quite effective; on a chronic basis, however, partial pressure of carbon dioxide should be kept at 32 to 38 mm Hg to avoid decreasing brain cell perfusion. Indomethacin is also a cerebral vasoconstrictor and carries the same risk to adequate perfusion. Elevating the head of the bed to approximately 30° and avoiding flexion or turning of the neck to prevent jugular kinking are effective in reducing ICP. Pain, fever, shivering, and seizures must be managed aggressively. Because the goal is to ensure perfusion while reducing ICP, maintaining and even elevating systemic MAP by appropriate use of fluid therapy and pressor agents are key therapeutic measures.

Diuretic agents, such as mannitol 0.25 to 1 g/kg bolus, which is a form of osmotherapy, may also be useful through reducing brain volume by removing water, changing the rheologic characteristics of blood, and producing reflex vasoconstriction. Caution is advised, however. Mannitol used as a chronic infusion can eventually cross the blood-brain barrier and draw more fluid into the brain. It is most effective in patients in whom the blood-brain barrier is intact. Hypertonic saline (3%) 2 to 6 mL/kg bolus followed by 0.1 to 1.0 mL/kg per hour as a continuous infusion may be an effective alternative. Serum osmolarity greater than 320 mOsm/kg can result in renal failure. Generally, such effects can be avoided by giving diuretic agents at intervals as a bolus and titrating up to the ICP-reducing dose. In some instances these agents are used to counter ICP plateau waves or increased pressure associated with endotracheal suctioning or other procedures.

In the child with severe refractory increased ICP, especially if secondary to an acute focal process, a barbiturate (eg, pentobarbital) or the benzodiazepine midazolam can be given as a continuous IV infusion with appropriate monitoring of brain electrical activity, serum levels, and systemic and brain perfusion pressures (Box 79.3). These agents may serve to reduce brain metabolism without significantly impairing vascular autoregulation; however, potential risks include reducing cardiac output and inducing associated infections, particularly pneumonia. Xenon CT measures multiple areas of local blood flow and may be a useful bedside technique to help specify targeted therapies. Decompressive craniotomy or craniectomy in early severe trauma in small series of patients has been associated with good outcomes in up to 50%. Hypothermia has not been useful in the management of cardiac arrest in the pediatric patient. Numerous "neuroprotective" agents continue to be studied as means of slowing metabolism and the resulting excitotoxic glutamatergic damage and thereby reduce cytotoxic edema and spread of the volume of irreversibly damaged brain tissue into the surrounding penumbra of damaged but not dead brain.

Prognosis

The overall mortality rate for children brought to an emergency room with TBI is 4% to 5%. Most of these children die from increased ICP. Disability occurs in many of the survivors, but the extent of disability may not be known for months to years

Box 79.3. A Simplified Intensive Care Interventions Protocol for the Child With Increased Intracranial Pressure

- Attend to airway, breathing, and circulation; intubation for airway control for GCS score <8.
- Keep head of bed elevated to 30°.
- Neurosurgical consultation to consider ICP monitor for the patient with GCS score <8.
- Maintain normal or elevated systemic blood pressure, normal temperature, and normal serum glucose level.
- Continuous general and local anesthesia, sedation, muscle relaxants, and anticonvulsant agents.
- Control hyperventilation to $Paco_2$ at 32–38 mm Hg and provide supplemental oxygen and PEEP as necessary to maintain Pao_2 > 90 mm Hg.
- Dexamethasone 0.5 mg/kg (maximum of 10 mg) every 6 hours if evidence exists of vasogenic edema on a brain imaging study.
- If an ICP monitor is present, target cerebral perfusion pressure at 40–50 mm Hg (age ≥5 years) and 50–60 mm Hg (age 6–17 years).
- If ICP progressively rises, pressure waves >20 mm Hg last longerthan 5 minutes, or any pressure in the first 24 hours is >30 mm Hg, give 3% saline 5 mL/kg. Alternatively, give mannitol 250–1,000 mg/kg IV. This may be repeated to maintain serum osmolality at 300–320 mOsm.
- If 3% saline or mannitol needs repeating in <6 hours or osmolality is >320 mOsm:
  Give pentobarbital 5 mg/kg IV, then 2 mg/kg/hour IV monitoring to blood level of 25–35 mg/mL, burst-suppression pattern with 10 seconds between bursts on EEG, and cardiac index >2.7 L/minute/m^2.
  Or
  Give midazolam by titrating the dose upward starting at 0.1 mg/kg/hour IV to the same EEG criteria and limited by the same cardiac index criteria.
- Particularly in trauma cases in which the cerebral lesion is primarily unihemispheric and pressure is rapidly increasing, hemicraniectomy should be considered.

Abbreviations: EEG, electroencephalography; GCS, Glasgow Coma Scale; ICP, intracranial pressure; IV, intravenous; $Paco_2$, partial pressure of carbon dioxide; Pao_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure.

afterward because recovery can be quite slow. The 10-year survival rate for all children with brain tumor is 70%. In children with encephalopathy with increased ICP with systemic hypotension, hyperglycemia, or disseminated intravascular coagulation, the prognosis for death or disability is worse regardless of cause. Some types of lesion, such as ischemia, can generate increased ICP that may advance too rapidly for therapeutic measures to take effect or are refractory to medical or surgical treatment, resulting in irreversible brain tissue damage or death. However, children can recover from increased ICP if brain perfusion pressure is adequately maintained and the underlying brain lesion generating the increased pressure can be resolved.

CASE RESOLUTION

The boy has focal signs and symptoms referable to the posterior fossa brain stem and cerebellum as well as symptoms of increased ICP. Emergent CT shows subacute hydrocephalus resulting from obstruction of CSF flow produced by a large mass in the cerebellum and brain stem on the left side. He begins taking dexamethasone and experiences some relief of increased ICP symptoms. Two days later a ventriculostomy is placed and the mass, which is found to be a medulloblastoma, is surgically removed. Because the ICP eventually subsides over the next few days and decreasing ventriculomegaly is evident on CT, a ventriculoperitoneal shunt is not required and the ventricular drain is removed. The boy's recovery is otherwise uneventful, and he begins the staging evaluation for medulloblastoma radiotherapy and chemotherapy.

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CHAPTER 80

Management of Dehydration in Children: Fluid and Electrolyte Therapy

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CASE STUDY

A 2-year-old boy presents to your office after 2 days of vomiting and diarrhea. His siblings were both ill a few days previously with similar symptoms. At a well-child visit 2 weeks previously, his weight was 12 kg (26.5 lb). Today his weight is 10.8 kg (23.8 lb). He has a pulse of 130 beats per minute, respiratory rate of 28 breaths per minute, and blood pressure of 85/55 mm Hg. He is alert and responsive but appears tired. He has dry mucous membranes, no tears with crying, and slightly sunken-appearing eyeballs. His capillary refill is 2 seconds. He urinated a small amount approximately 6 hours before this office visit. Despite his mother's best efforts in your office, the patient has vomited all the oral rehydration therapy given to him. You draw blood for analyzing electrolyte, blood urea nitrogen, and creatinine levels and initiate intravenous rehydration by administering 2 boluses each of 240 mL normal saline (0.9% sodium chloride solution).

Questions

1. How is the magnitude of dehydration in a child assessed?
2. What are the different types of dehydration?
3. How is the type and amount of fluid required by the dehydrated child determined?
4. How is renal status assessed in the dehydrated child?
5. What is the role of electrolyte and acid-base laboratory tests in the evaluation of the dehydrated child?

Dehydration resulting from gastrointestinal (GI) and other disorders, especially diarrhea, is among the most common medical problems encountered in children younger than 5 years. During the past 50 years or more, the usual therapy for children who are hospitalized with dehydration has been to administer intravenous (IV) fluids starting with 1 or 2 boluses of normal saline (NS; 0.9% sodium chloride [NaCl] solution at 20 mL/kg). This is followed by the administration of a sodium (Na^+) solution of variable concentration (usually 0.45% NaCl) mixed with 5% dextrose over the next 24 to 48 hours until the child is able to take oral fluids. The exact amount of fluid and electrolytes is calculated using complicated formulas to provide maintenance fluids and correction of remaining deficit (ie, deficit therapy). The calculation of maintenance therapy was first recommended in the 1950s, but more recently it has been suggested that dehydration management should focus on rapid restoration of extracellular fluid (ECF deficit) followed by oral rehydration therapy (ORT), and traditional calculations of fluid deficits should be abandoned. Alternatively, pediatric nephrologists and intensivists have recommended that physicians forgo sodium calculations in hospitalized children and rely solely on isotonic NS (0.9% NaCl solution) for management. Although this chapter incorporates these suggestions where appropriate, it describes the traditional approach to maintenance and deficit therapy because an understanding of the pathophysiology of dehydration helps in the treatment not only of the dehydrated child but also of children with other types of fluid and electrolyte disorders.

Epidemiology

Over the past 30 years, hospital admissions and mortality resulting from diarrhea and dehydration have decreased worldwide; nevertheless, diarrhea remains 1 of the leading medical problems in children younger than 5 years. According to the Centers for Disease Control and Prevention, more than 200,000 hospitalizations and 300 deaths of children occur each year in the United States resulting from diarrhea. Additionally, diarrhea is responsible for 2 to 3 million outpatient visits each year and contributes to 10% of all hospital admissions.

Maintenance Fluid and Electrolyte Requirements

The body has a maintenance fluid requirement to replace daily normal losses that occur through the kidney, intestines, skin, and respiratory tract. Of the various methods used to determine fluid needs, the most common is the caloric method, also called the Holliday-Segar method, which is based on the linear relationship between metabolic rate and fluid needs. For every calorie expended in metabolism, a child requires approximately 1 mL of water. Metabolic rate in children is a function of body surface area. Infants, with their higher relative surface areas per unit of body weight, have higher metabolic rates and, therefore, higher fluid requirements per unit weight compared with older children and adults. As the child grows, the relative surface area decreases, as do the metabolic rate and fluid requirement per unit weight. Using this relationship, maintenance fluid needs can be calculated for the healthy child using the method outlined in Table 80.1. These calculations of fluid needs are often used to determine the amount of IV fluids provided to a hospitalized child or to calculate the approximate amount of fluid a healthy child requires orally to maintain hydration. These calculations may not be appropriate for children who are critically ill, however, some of whom require fluid restriction and others of whom may have increased fluid needs. Moreover, the caloric method makes no allowance for extra fluid needed for weight gain, growth, activity, or pathophysiological states that increase fluid needs (eg, fever). The fluid requirement derived from this method is valid to determine the daily fluid need for an essentially healthy child. Thriving infants normally drink more fluid than indicated by this method. On average, a growing infant may take 150 to 200 mL/kg per day of milk (human milk or infant formula) as desired to support the average weight gain of 30 g (1.1 oz) per day usually observed in the first few months after birth.

Replacement of normal daily losses of electrolytes is considered when a child is not able to take adequate nutritional intake orally (as in the example in Box 80.1, in which the child receives nothing orally in preparation for surgery). Electrolyte quantities usually are expressed as milliequivalent (mEq) or millimole (mmol) amount per 100 mL of fluid required. Traditionally, the recommended sodium requirement for a healthy child is 3 mEq/100 mL fluid required (approximately 0.2% NaCl or 0.25 NS), and the potassium (K^+) requirement is 2 to 2.5 mEq/100 mL of fluid (see Box 80.1, part B, for sample calculation and IV order). Potassium should be administered only after ensuring adequate renal function. These estimations of sodium and potassium requirements are meant to replace normal daily losses and would not be adequate in the setting of increased electrolyte losses that can occur in a number of pathologic conditions (eg, diarrhea). Additionally, increased attention has recently been given to the risk of hyponatremia and related complications in hospitalized ill children.

Relatively healthy, well-nourished children receiving IV fluids for a brief period (ie, 1–2 days) during hospitalization do not routinely require supplementation with other electrolytes, such as calcium and magnesium. However, it is important to realize that standard IV fluids containing 5% dextrose, sodium chloride, and potassium chloride provide only minimal caloric needs and do not adequately support weight gain or provide other necessary nutrients. The child who requires prolonged IV therapy because of inadequate GI tract function should receive total parenteral nutrition to better meet the child's caloric and nutritional needs.

Table 80.1. Caloric (ie, Holliday-Segar) Method of Determining Maintenance Fluid Requirements in Healthy Children

Weight	*Maintenance Fluid Requirement for 24 Hours*
<10 kg	100 mL/kg/day[a] or 4 mL/kg/hour
11–20 kg	50 mL/kg/day for each kg >10 kg + 1,000 mL (fluid requirement for first 10 kg) or 40 + 2 mL/kg/hour for each kg between 11 and 20 kg
>20 kg	20 mL/kg/day for each kg >20 kg + 1,500 mL (fluid requirement for first 20 kg) or 60 + 1 mL/kg/hour for each kg >20 kg

[a] Excluding neonates and preterm infants.

Box 80.1. Example of Fluid Calculations[a]

Part A

Case: A boy weighing 22 kg is given nothing orally in preparation for an elective abdominal surgery. The following calculation is used to determine the appropriate amount of IV fluid per hour to administer as he awaits surgery.

- For first 10 kg: 100 mL/kg/day × 10 kg = 1,000 mL
- For next 10 kg (to get to 20 kg): 50 mL/kg/day × 10 kg = 500 mL
- For next 2 kg (to get to 22 kg): 20 mL/kg/day × 2 kg = 40 mL

1,000 mL + 500 mL + 40 mL = 1,540 mL/24 hour

IV rate per hour = 64.2 mL/hour (with a healthy child, round off to 65 mL/hour for ease of administration)

Part B

Question: How much Na^+ and K^+ should this patient receive in his IV fluids?

Answer:

Based on physiologic losses: 3 mEq Na^+/100 mL (1 dL) of fluid = 3 mEq × 15.4 dL = 46.2 mEq Na^+/day in 1,540 mL of water or 30 mEq NaCl/L

2.0 mEq K^+/100 mL (1 dL) of fluid = 2.0 × 15.4 = 30.8 mEq K^+/day in 1,540 mL of water or 20 mEq KCl/L

Therefore, IV order for this patient is as follows:

D5 0.2% NaCl (or 0.25 NS) with 20 mEq KCl/L to run at 65 mL/hour

Abbreviation: D5 = 5% dextrose water; IV, intravenous; K^+, potassium; KCl = potassium chloride; Na^+, sodium; NaCl, sodium chloride; NS, normal saline.

[a] Even though in this example the calculations for sodium concentration in the IV fluid is physiologic, recent American Academy of Pediatrics guidelines recommend use of NS with 5% dextrose preoperatively to prevent potential postoperative hyponatremia.

Alterations in Fluid Needs in Illness

Several conditions can influence fluid requirements. Conditions that increase a patient's metabolic rate (eg, fever) will also increase a patient's fluid requirement. A child's metabolic rate is increased 12% for every 1°C temperature elevation above normal. Most otherwise healthy children with free access to fluids will increase their own intake to account for increased needs when febrile. Other less common hypermetabolic states, such as thyrotoxicosis or salicylate poisoning, may have an even more dramatic effect, perhaps increasing metabolic rate by 25% to 50% over maintenance. In these cases and for children who are dependent on others to provide their fluids, the physician must be aware of the magnitude of increased need and provide supplemental fluids to avoid dehydration.

Other conditions may decrease a child's fluid requirement. In hypometabolic states, such as hypothyroidism, metabolic rate and fluid needs are decreased by 10% to 25%. Fluid requirements are decreased by 10% to 25% in high environmental humidity unless the ambient temperature is also high and results in visible sweating. In these situations, a healthy child with normal renal function given extra fluid beyond what is needed can, within limits, effectively excrete any excessive intake. The child with renal failure, however, poses a special challenge for the physician in the management of fluid and electrolytes. When a child cannot adequately excrete excessive fluid intake, this fluid can accumulate and result in complications such as congestive heart failure and pulmonary edema. Without functioning kidneys, only insensible fluid losses need replacing. Insensible losses occur primarily through the skin and respiratory tract; they account for approximately 40% of maintenance fluid needs. However, fluid needs for patients with renal failure usually are estimated to be 30% of the maintenance requirement, with additional fluids provided if necessary. Limiting fluids avoids the accumulation of excessive fluids that may require dialysis for removal.

Fluid requirements may also be decreased under circumstances in which arginine vasopressin (AVP; also called antidiuretic hormone) is increased. In addition to hypovolemia or hypertonicity (ie, hyperosmolality), AVP release is also stimulated by pain, nausea, surgery (ie, in the postoperative period), central nervous system (CNS) infections (eg, meningitis, encephalitis), severe pneumonia or respirator use, and certain medications, including thiazide diuretics, chemotherapeutic agents, and selective serotonin reuptake inhibitors. Arginine vasopressin release in the absence of hypovolemia or hypertonicity results in hyponatremia and is referred to as *syndrome of inappropriate antidiuretic hormone secretion*. In patients with this syndrome, fluid restriction as well as administration of fluids with a higher sodium concentration may be indicated.

The most appropriate sodium concentration of IV fluids for the hospitalized child admitted to a pediatric intensive care unit or in the postoperative patient is controversial. Over the past 25 years, most such children have been maintained on a solution containing 5% dextrose water in half NS (D5 0.5 NS) or lower sodium concentrations (D5 0.25 NS). Studies suggest that because the kidney retains free water in response to excessive AVP in these children, they are at risk for hyponatremia, hyponatremic encephalopathy, brain stem herniation, permanent brain damage, or death. Recently, some pediatric nephrologists and intensivists have recommended forgoing sodium calculations in hospitalized very sick children and instead relying solely on isotonic fluids. Others have cautioned that physicians must make certain that the new recommendations to use isotonic fluids do not result in excessive congestive heart failure or hypernatremia before abandoning previous practices. Regardless of the approach used, close attention to the type and quantity of fluids provided, quantity of body fluid output, weight change, and serial electrolyte assessments are important in the management of all sick children, and fluid and electrolytes must be individualized to each patient to prevent serious complications.

Pathophysiology

Dehydration is among the most common pathophysiological alterations in fluid balance encountered in pediatrics. Although strictly speaking, *dehydration* means deficit of water only, most children with dehydration have lost water and electrolytes. Dehydration can result from diminished intake, excessive losses through the GI tract (eg, diarrhea, vomiting), excessive losses from the kidney or skin (eg, polyuria resulting from osmotic diuresis in uncontrolled diabetes), or a combination of these factors.

Children are at increased risk for episodes of dehydration for many reasons. Infants and young children have 2 to 4 times the body surface area per unit body weight compared with adults and as a result have relatively higher fluid needs. It is therefore much easier for children to become dehydrated in the setting of decreased intake or increased losses that often accompany common childhood illnesses. For example, acute gastroenteritis, which is common in young children, often results in anorexia, recurrent vomiting, and frequent or large-volume stools, with proportionately more severe fluid loss than in older children and adults. Additionally, infants and young children are dependent beings who are unable to increase their own fluid intake in response to thirst and must rely on others to provide their fluid needs. If these fluid needs are not met or are underestimated, a child can easily become dehydrated.

Dehydration is classified as isotonic, hypotonic, or hypertonic. These terms often are used interchangeably with isonatremic, hyponatremic, and hypernatremic, respectively. The latter terms reflect the sodium content of the ECF that largely determines serum osmolality in the otherwise healthy dehydrated child. Acute isotonic or isonatremic dehydration (serum Na^+ 135–145 mEq/L), which is the most common type of dehydration, involves net loss of isotonic fluid containing sodium and potassium (Figure 80.1, top). In diarrhea-related dehydration, sodium, the primary ECF cation, is not only lost from the body but also shifts into the intracellular fluid (ICF) compartment to balance the loss of potassium, because potassium losses from cells generally are not accompanied by intracellular anionic losses in acute dehydration. The sodium that has shifted into the ICF compartment will return to the ECF compartment during rehydration as potassium is being replenished, by the action of sodium/potassium adenosinetriphosphatase (ATPase). No net loss of fluid from the ICF occurs in this

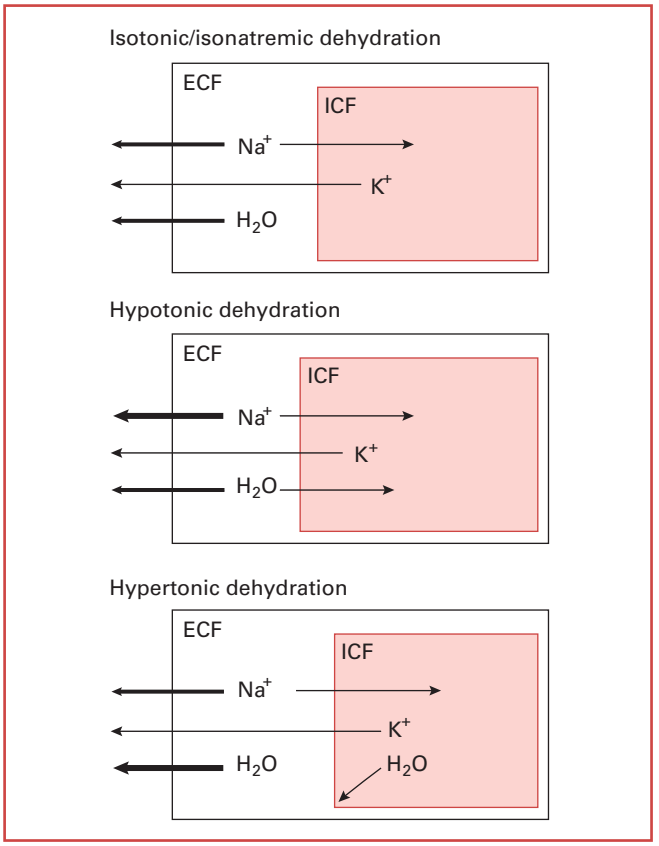

Figure 80.1. Pathophysiology of various types of dehydration. Top, Isotonic/isonatremic dehydration. Middle, Hypotonic dehydration. Bottom, Hypertonic dehydration. Abbreviations: ECF, extracellular fluid; H_2O, water; ICF, intracellular fluid; K^+, potassium; Na^+, sodium.

process; the total water deficit in dehydration comes primarily from the ECF, although some investigators have suggested, in the absence of valid data, that two-thirds of the losses come from ECF and one-third from ICF.

A variety of mechanisms exist by which hyponatremia (serum Na^+ <135 mEq/L) occurs in association with dehydration. In hypotonic or hyponatremic dehydration, the ECF volume is compromised to a greater degree than in isotonic dehydration because of osmotic shifts of ECF into the cells, resulting in more severe signs of dehydration (Figure 80.1, middle). Hypotonic dehydration typically occurs in children with gastroenteritis in the setting of excessive sodium losses in stool and oral fluids replacement with a reduced amount of sodium (ie, water, low-sodium beverages [eg, juice, tea]). Furthermore, the kidneys often retain free water (ie, excrete a concentrated urine) despite hyponatremia, because AVP is stimulated by the decreased effective circulating volume in such settings. Intravascular volume depletion seems to be a potent stimulus for AVP release, overriding the AVP suppressive effect of hypotonicity/hyponatremia. The result is that serum sodium levels are further decreased because of dilution. Hypotonic dehydration also may occur as the result of excessive loss of sodium (relative to body water) in stool (eg, cholera) or in the urine (eg, adrenogenital syndrome, cerebral salt wasting, pseudohypoaldosteronism, other salt-wasting renal disorders). This is the most dangerous form of dehydration because it can result in cerebral edema and eventually, brain herniation.

Hypertonic or hypernatremic dehydration (serum Na^+ >145 mEq/L) occurs when net loss of water exceeds that of solute loss (Figure 80.1, bottom). It usually is seen in clinical conditions in which rapid loss of hypotonic fluid in stool, vomit, or urine occurs, accompanied by failure of adequate water intake because of anorexia or vomiting. Fever or hyperventilation, if present, may intensify the disproportionate loss of water. Occasionally, hypertonic dehydration may be caused by excessive solute intake. Urinary excretion of excess solute obligates loss of large volumes of water, resulting in dehydration. The history may reveal that the child was accidentally fed a high sodium solution because of incorrect mixing of oral rehydration packets or concentrated formula. In hypertonic dehydration, shift of fluid from the ICF to the ECF occurs to attain osmotic balance. As such, the ECF volume is somewhat spared at the expense of the ICF, and signs of dehydration may be delayed. However, fluid loss from the ICF results in intracellular dehydration, the most serious effect of which can occur in the brain. If hypernatremia occurs rapidly, not only does a decrease in brain size occur, but a fall in cerebrospinal fluid pressure occurs as well resulting from diffusion of water from cerebrospinal fluid to the blood. As the brain shrinks, the bridging veins within the skull may stretch and even tear, resulting in intracranial hemorrhage or other complications. If the hypertonic state manifests more slowly, brain cell size may initially shrink minimally but will gradually return to normal size even with continued hypernatremia. Preservation of the brain cell volume despite hypernatremia is thought to be caused by the generation of idiogenic osmoles (eg, myoinositol, trimethylamines, taurine, and other amino acids) that prevent water loss and attract water back into the cell and thus maintain cell volume. Rehydration of the patient with hypernatremia must occur slowly and cautiously to avoid brain cell swelling (Figure 80.2). In the child with hypertonic dehydration, on clinical examination the skin may sometimes feel "doughy" because of intracellular dehydration. This finding, however, is inconsistent even when evaluation is done by an experienced pediatrician; thus, clinical examination of the skin should not substitute for serum sodium measurements in the diagnosis of hypernatremia.

Evaluation

History

In addition to signs and symptoms of the current illness, the history should focus on the cause of dehydration. The parent or guardian should be questioned about the type and amount of oral intake; the duration, quality, and frequency of vomiting or diarrhea; whether blood is present in the stool; the presence or absence of fever; frequency of urination; and whether a recent pre-illness weight is known for the child (Box 80.2). Changes of mental status reported by a parent or guardian is of particular concern because this can occur as the result of significant electrolyte (eg, sodium) disturbance, marked dehydration, or other serious infection or illness. The most accurate means of assessing the degree of dehydration is to compare current weight with a recent pre-illness weight. In acute

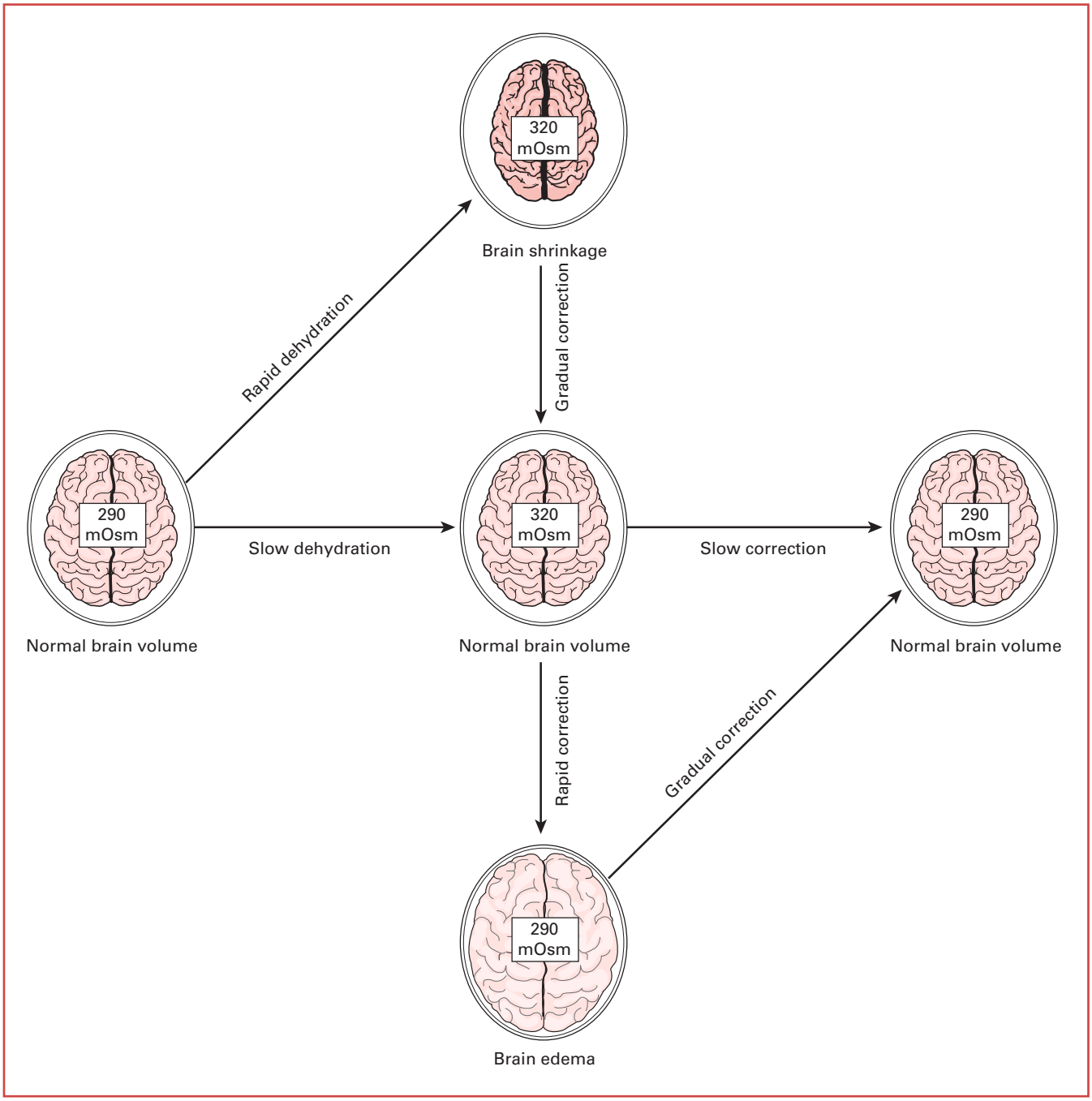

Figure 80.2. Illustration of the steps in managing hypertonic dehydration showing the effects on brain volume of rapid versus slow development of hypernatremia and the results of rapid versus slow correction of hypernatremia.

dehydration, weight loss is primarily the result of fluid loss. The difference between pre-illness and current weight can be used to determine the degree of the fluid deficit.

Physical Examination

An important goal of the physical examination of the dehydrated child is to assess the degree of dehydration. In the process, vital signs, including blood pressure and a current weight, should be obtained. Specific attention should be paid to the general appearance of the child and, in particular, whether the child is ill-appearing, listless, or less reactive. In addition to the usual components of the physical examination, it is important to assess for the following factors: whether the oral mucosal membranes appear tacky or dry, whether tears are present or absent, if tenting of the skin is present (ie, tenting remains after the skin is pinched between 2 fingers), and perfusion status of the extremities. In the process, it is important that the physician recognize whether shock is present, because this is a life-threatening condition requiring emergent treatment (see Chapter 74).

If comparison to an accurate recent pre-illness weight is not possible, the physician must rely on vital signs as well as clinical signs and symptoms to assess the degree of dehydration (Table 80.2). In infants

Box 80.2. What to Ask

Dehydration

- Has the child been vomiting and/or having diarrhea?
- How many stools has the child had, and how large was each stool?
- How many times did the child vomit, and how much vomitus occurred each time?
- Does the child have fever?
- What type fluid has the child been drinking?
- Has the child been urinating? How many wet diapers did the child have in a day?
- How much did the child weigh at the last visit to the physician?
- Has your child's behavior or level of alertness changed from normal?

and young children (ie, younger than 5 years), the estimated fluid loss for mild dehydration is less than or equal to 5% deficit of body water; moderate dehydration, 6% to 9%; and severe dehydration, 10% to 15%. The corresponding numbers for estimated fluid loss in children 5 years and older are 3%, 6%, and 9%, respectively. A variety of clinical signs have been proposed to evaluate the degree of dehydration—some more valid and reliable than others. A systematic review found that assessment of capillary refill was the most useful single sign in detecting dehydration of 5% or more. Capillary refill is assessed by placing brief pressure on the distal palmar aspect of a fingertip and assessing the amount of time for the blanched area to refill; normal is considered less than or equal to 2 seconds. Two other single signs found to be important in predicting dehydration of 3% to 5% or more were abnormal skin turgor (ie, tenting) and respiratory disturbance, in particular *hyperpnea* (ie, deep, rapid breathing without other signs of respiratory distress) suggestive of acidosis. Generally, the more signs that are present, the greater the severity of dehydration; however, a combination of prolonged capillary refill, absent tears dry mucosal membranes, and general ill appearance may be more diagnostic than tenting and hyperpnea combined in identifying the child with more than mild to moderate dehydration.

Laboratory Tests

Laboratory tests typically are not indicated in the child who presents with mild dehydration. The dehydrated child who is treated with IV fluids after a failed attempt at oral rehydration either at home or in the emergency department should undergo initial assessment of serum electrolyte, blood urea nitrogen, and creatinine levels. Initial and serial measurements of these values also should be performed during rehydration in the child with shock, severe dehydration, or decreased urine output who does not improve after initial restoration of intravascular volume; with a history and clinical findings inconsistent with straightforward isotonic dehydration; or who is found to have dysnatremia (ie, serum sodium outside the normal range of 135–145 mEq/L, whether too low or too high). Dehydration in association with dysnatremia can have serious complications, and treatment requires special considerations. Hemolytic uremic syndrome, although uncommon, should be considered in any child with gastroenteritis, particularly with a history of grossly bloody stool, who also has decreased urine output.

Very ill children may require an arterial blood gas measurement to more accurately assess their acid-base status; in others, assessing serum electrolyte levels is sufficient. The usual acid-base derangement in the moderately dehydrated child is a non-anion gap acidosis with decreased serum bicarbonate and hyperchloremia resulting

Table 80.2. Clinical Assessment of Magnitude of Dehydration

Clinical Sign	*Mild Dehydration*[a]	*Moderate Dehydration*	*Severe Dehydration*[b]
Loss of body weight			
<5 years	≤5%	6–9%	≥10%
≥5 years	3%	6%	9%
Skin turgor	Normal to slightly reduced	Decreased	Markedly decreased (ie, tenting)
Skin color and temperature	Pale or normal[a]	Ashen, cool	Mottled, cool
Dry mucous membranes	±[a]	+	++
Absent tears	±	+	++
Sunken eyeballs	±	+	++
Increased pulse	±[c]	+[c]	++ (may be thready)
Blood pressure	Normal	Normal Postural decrease ±	Reduced (ie, in late shock)
Urine output	Normal or reduced[c]	Oliguria[c]	Oliguria, anuria
Capillary refill time	Slightly prolonged[c]	Prolonged[c]	Prolonged

Abbreviations: ++, certain to occur; +, likely to occur; ±, may occur.

[a] In mild dehydration, may be only a history of fluid loss in the form of diarrhea or vomiting without any of the signs of dehydration listed in this table.

[b] Often, such patients present with hypovolemic shock, need more intense treatment, and may require additional volume expanders (eg, colloids, blood products).

[c] Usually corrects with restoration of intravascular volume.

from bicarbonate losses in the stool. Additionally, the severely dehydrated child also may exhibit anion gap acidosis resulting from lactic acid or ketone accumulation in the peripheral tissues secondary to the decreased perfusion that accompanies hypovolemia. The exception is in infants with pyloric stenosis, who typically develop a hypokalemic, hypochloremic metabolic alkalosis.

Imaging Studies

Imaging studies, such as chest radiography, abdominal ultrasonography, and computed tomography, are indicated based on the suspected etiology of the dehydration.

Management

Fluid management of the dehydrated child involves consideration of 3 components: normal maintenance, deficit replacement, and the ongoing losses of fluid and electrolytes incurred during the present illness. Most commonly, ongoing losses result from continued vomiting and diarrhea. Losses from diarrhea can be estimated at 10 mL/kg per stool and for vomiting at 5 mL/kg per episode. Other forms of ongoing losses that occasionally must be considered and replaced include those associated with burns, gastric secretion suctioned via nasogastric tube, hyperventilation, or prolonged fever. The estimation of the child's fluid and electrolyte needs and losses are almost always an approximation and require close follow-up, reassessment, and readjustment throughout treatment. At the very least, monitoring during treatment for dehydration requires regular assessment of vital signs, body weight, intake, and output.

Fluid given to the dehydrated child may be provided enterally or parenterally. Whenever possible, oral replacement therapy using oral rehydration solution (ORS) is preferred for the child with mild dehydration and for most children with moderate dehydration. Parenteral fluid therapy should be used in the child with more severe dehydration, in the setting of failure of oral therapy (eg, resulting from intractable vomiting or lethargy) despite an adequate trial, in the child in shock or impending shock, or in the child with a suspected anatomic defect, such as pyloric stenosis or ileus.

Parenteral Fluid Therapy

The parenteral management of moderate or severe dehydration can be divided into 2 phases: an initial phase (first 1–2 hours) and the main phase of rehydration. The aim of the initial phase is to restore intravascular volume, thus improving perfusion and renal function and reversing tissue hypoxia, metabolic acidosis, and increased AVP. Regardless of the type of dehydration (ie, isotonic, hypertonic, hypotonic), NS (0.9% NaCl) at 20 mL/kg per hour generally provides the most rapid and effective means of expanding the intravascular volume at acute presentation. If shock is present or imminent, treatment is more aggressive (see Chapter 74). The child should in rapid succession receive 2 to 4 boluses of 20 mL/kg of NS given over 20 to 30 minutes each. After each bolus, the child should be reassessed, and if signs and symptoms of intravascular depletion persist, the next IV bolus of 20 mL/kg of NS should be given over 20 to 30 minutes and the child admitted to the hospital for further careful evaluation, including assessment for other causes of shock (eg, sepsis). Rapid restoration of ECF volume with up to 4 boluses of NS, if necessary, in the first 4 hours is currently recommended. The physician must take care not to give excessive fluids to a child with cardiac compromise, because doing so could precipitate congestive heart failure. Administration of excess fluids also results in decreased AVP/antidiuretic hormone levels and the chances of hyponatremia in subsequent therapy even if 0.45% NaCl (0.5 NS) solutions are used rather than NS to correct the remaining deficit and maintenance therapy. The validity of rapid restoration of ECF volume with up to 4 boluses of NS, however, has not been substantiated compared with the past standard rehydration therapy in which typically only 1 or 2 boluses were used. All ORT fluids generally use hypotonic containing sodium concentrations of 45 to 75 mEq/L.

During the second phase of rehydration, the remaining fluid and electrolyte deficits are replaced based on the magnitude of these losses. These replacements are in addition to the daily maintenance requirements as well as any ongoing losses, as discussed previously, but must take into consideration the NS boluses administered during the initial phase, which may have already restored a substantial portion of the total fluid deficit. Each 20 mL/kg fluid bolus corrects 2% dehydration. Thus, in the child with moderate dehydration use of 3 boluses of 20 mL/kg of NS would correct 6% dehydration, with the result that the child may no longer have any remaining fluid deficit. Various protocols exist to restore fluid and electrolyte deficits, and approaches to treatment of dehydration vary by institution. Many of the differences in rehydration strategies lie in the composition of treatment fluid and the rate at which it is administered. Some physicians prefer to administer one-half of the total fluid needs over the first 8 hours and the remainder over the next 16 hours, whereas other physicians prefer to replace the fluid at the same rate over the entire rehydration period. The latter method is presented in the case resolution at the end of the chapter. Usually the fluid deficit is replaced within 24 hours, although noteworthy exceptions exist. The management of dehydration associated with *dysnatremia* (ie, abnormally low or high serum Na^+) should entail slower return (12 mEq serum Na^+ change per 24 hours or 0.5 mEq change per hour) to a normal range and may require 48 to 72 hours for correction.

Sodium replacement in the child with dehydration depends on the type of dehydration. In the management of isotonic dehydration, some physicians elect to replace the entire fluid deficit with NS, whereas others use a saline solution containing 110 mEq Na^+/L, and still others use 0.5 NS (77 mEq Na^+/L). We recommend NS (154 mEq Na^+/L) to replace the fluid deficit (see Case Resolution for example). This amount of sodium is somewhat more than the actual loss of sodium to the environment, which is closer to 110 mEq Na^+/L, because during isotonic dehydration some sodium lost from the ECF is shifted intracellularly to balance potassium losses and thus returns to the ECF during rehydration. To calculate the ongoing losses, although the content of excreted body fluids can be analyzed for electrolyte content for more exact replacement, the diarrheal stools are commonly replaced with 0.5 NS at 10 mL/kg

per stool. (This amount should be adequate in sodium content for most patients because diarrhea secondary to rotavirus contains approximately 30–40 mEq Na^+/L and enterotoxigenic *Escherichia coli*, 50–60 mEq/L; however, sodium stool losses in cholera are 90–120 mEq/L.)

Management of Electrolyte Disturbances

Hypernatremia and Hyponatremia

In hypernatremic/hypertonic dehydration, the patient is considered to have a relative free water deficit but usually has lost not only body water but also some sodium. The amount of free water required to restore serum sodium to normal (eg, 145 mEq/L is desired serum Na^+) is calculated as follows:

$$[\text{patient's weight in kg}] \times [\text{actual serum } Na^+ - 145] \times 4 \text{ mL/kg}$$

For serum sodium greater than 170 mEq/L, 3 mL/kg of free water is estimated to decrease the sodium to the desired level, in which case the 4 mL/kg shown in the equation is changed to 3 mL/kg. The quantity of free water provided by this equation is only part of the patient's total needs. The remainder of the patient's fluid needs include isotonic losses that occurred during the dehydration process, ongoing losses, and maintenance fluids as well. Hypertonic dehydration is corrected slowly to avoid cerebral edema, which can result in brain stem herniation and death. In hypernatremia, the various equations used for phase 2 of therapy often calculate the sodium concentration of the final solution considering the amount of free water to achieve isotonicity. We recommend initially providing 0.9% NaCl in 5% dextrose (a higher content of sodium than calculated by various equations) to ensure a slow rate of serum sodium decline and later decreasing the sodium concentration to 0.45% NaCl if the serum Na level remains high 24 to 48 hours after this treatment is begun. Serial monitoring of electrolytes at least every 6 hours and as necessary is important to ensure that the sodium level is decreasing at the expected slow rate and is not decreasing so quickly as to result in life-threatening CNS complications.

Management of hyponatremia/hypotonic dehydration also poses challenges. In addition to isotonic losses, additional sodium loss may have occurred. The amount of additional sodium (in mEq) to correct the serum sodium into a normal range (desired Na^+ level [eg, 135 mEq/L]) historically has been calculated using the following equation (where 0.6 represents the body space affected by Na^+ changes):

$$[\text{patient's weight in kg}] \times [135 - \text{actual } Na^+ \text{ level}] \times 0.6$$

This amount of sodium represents an additional need beyond a patient's isotonic losses, ongoing losses, and maintenance requirements. Although precise calculations of sodium requirement to manage hypotonic dehydration may be desirable, in most patients with hyponatremia treatment with NS (0.9% NaCl) in 5% dextrose is adequate for gradual correction of the hyponatremia. The use of hypertonic saline (3% containing 513 mEq Na^+/L) is generally reserved for the child with symptomatic hyponatremia (eg, a child who is seizing) or in the setting of serum Na level of less than 120 mEq/L. Hypertonic saline is administered as 3.0 mL/kg of 3% saline given by IV over 15 to 30 minutes or until seizures stop. This volume of 3% saline raises the serum sodium approximately 2.5 mEq/L. Based on a volume of 3.0 mL/kg of 3% saline, the child should receive volume sufficient to bring up the serum Na level to above 120 mEq/L, which is considered to be the safe level, at which improvement in serious signs and symptoms are anticipated. Recalculation is done 4 hours after the initial 3% NaCl infusion to determine the need for another infusion, if the level is still low or if there is no improvement in CNS-related symptoms. After a level of greater than 120 mEq/L is achieved or the patient is asymptomatic, any remaining deficit is corrected more slowly to avoid exceeding an increase of 12 mEq/L per 24 hours. A too rapid correction of serum sodium, particularly in the setting of long-standing hyponatremia, can potentially cause central pontine demyelination, manifested by disorientation and eventual coma.

As stated previously, hyponatremia in the hospitalized child can result from factors other than sodium loss. Arginine vasopressin release in response to hypovolemia, hypertonicity, or other stimuli followed by free water retention can result in dilutional hyponatremia (ie, water intoxication). Hyponatremia in infants given excessively diluted baby formula results from inadequate sodium intake and free water retention. Encephalopathy, brain stem herniation, and death occurring in hospitalized children with hyponatremia have been reported. The adverse effects of hyponatremia on the CNS are accentuated in the setting of hypoxemia. With rehydration and sodium administration, kidneys excrete relatively more dilute urine that can sometimes result in rapid and unpredictable increases in serum sodium levels, necessitating close monitoring of serum electrolyte levels. Consultation with a pediatric nephrologist or pediatric intensivist experienced in managing alterations in fluid and electrolyte balance is helpful.

Potassium Replacement

Potassium deficits are more difficult to determine, and no specific method exists for calculating the exact amount of potassium required by a dehydrated child. Additionally, as the acidosis that commonly accompanies moderate and severe dehydration corrects, potassium shifts intracellularly. What initially seems to be a normal serum potassium may fall into the hypokalemic zone, potentially resulting in adverse effects on neuromuscular and cardiac function. Frequent reassessment of serum potassium and adjustment of potassium content of the IV fluids may be necessary. Generally, after adequate urine output has been established, potassium may be added to the IV fluids to provide 3 to 4 mEq/kg per 24 hours. Usually, this need can be met by adding potassium chloride 20 mEq/L to the IV fluids. The child with decreased urine output or another indicator of renal impairment should not receive potassium until normal urine output has been restored. Hyperkalemia, which is a serious and life-threatening condition, may occur if a child is unable to excrete excess potassium via the kidney because of renal impairment.

Oral Rehydration

Oral rehydration therapy refers to specially prepared, balanced preparations of carbohydrates and electrolytes meant for oral consumption. Clinical trials have repeatedly shown ORT to be as efficacious as IV therapy in the treatment of the child with mild or moderate dehydration. Additional advantages of ORT over IV therapy are that it costs less, is noninvasive, and requires little technology. Oral rehydration therapy has been credited with the dramatic reduction in death associated with diarrhea in the developing world. In 2002, the World Health Organization and United Nations Children's Fund announced a new ORS with reduced osmolarity (proportionally lower Na^+ and glucose concentration) based on several clinical studies demonstrating less vomiting, lower stool output, and reduced need for IV fluids relative to the prior formulation.

In the United States, Pedialyte and generic equivalents are the most widely commercially available products. Flavored solutions and freezer pop preparations of these solutions are available and often are preferred by older children over the unflavored variety. Rice-based oral electrolyte solutions contain rice syrup solids as their source of carbohydrates. Electrolyte solutions with rice syrup solids may reduce stool output as well as replete fluid volume. It is not necessary to change to ORT in a breastfed child who is tolerating human milk; these children can continue to receive human milk for rehydration, although they may require shorter, more frequent feedings.

The composition of various ORSs is presented in Table 80.3. The cost of commercially available ORS may be prohibitive for some families. Given the simplicity of the ORS packet in the developing world and commercially available ORS in the developed world, these remain the first choice. Some solutions, such as fruit juices, ORSs, or chicken broth, do not contain the proper balance of sodium and carbohydrate to effectively rehydrate a dehydrated patient; however, these can be used at home for mild cases of diarrhea if the patient still tolerates oral fluids.

The amount of ORT fluid necessary for rehydration can be calculated in much the same fashion as for determining the parenteral fluid requirement for a dehydrated child (Table 80.4). However,

Table 80.3. Composition of Various Oral Rehydration Solutions

Solution	Carbohydrate (gm/L)	Sodium (mEq/L)	Potassium (mEq/L)	Base (mmol/L)	Osmolarity (mOsm/kg H_2O)
Appropriate for Rehydration					
Pedialyte	25	45	20	30	250
Enfalyte	30	50	25	33	160
World Health Organization–UNICEF oral rehydration solution (2002)	13.5	70	20	30	245
Not Appropriate for Rehydration					
Cola[a]	110	2	0	13	750
Apple juice[a]	120	3	32	0	730
Chicken broth[a]	0	250	8	0	500
Sports beverages	40	20	3	3	330

Abbreviation: UNICEF, United Nations Children's Fund.

[a] These fluids should be avoided because they have very high osmolality that can worsen diarrhea.

Table 80.4 Guidelines for Administration of Oral Solutions to Replace Deficit Over 4 Hours

	Mild Dehydration (3%–5%)		Moderate Dehydration (6%–9%)	
Weight (kg)	Total Volume Over 4 Hours	Volume per Administration	Total Volume Over 4 Hours	Volume per Administration
5	150–250 mL	5 mL every 5–8 min	300–450 mL	6–9 mL every 5 min
10	300–500 mL	6–10 mL every 5 min	600–900 mL	12–18 mL every 5 min
15	450–750 mL	10–15 mL every 5 min	900–1,350 mL	18–28 mL every 5 min
20	600–1,000 mL	12–20 mL every 5 min	1,200–1,800 mL	25–37 mL every 5 min
25	750–1,250 mL	15–25 mL every 5 min	1,500–2,250 mL	30–45 mL every 5 min
30	900–1,500 mL	18–30 mL every 5 min	1,800–2,700 mL	37–55 mL every 5 min
40	1,200–2,000 mL	25–40 mL every 5 min	2,400–3,600 mL	50–75 mL every 5 min

Reprinted with permission from Powers KS. Dehydration: isonatremic, hyponatremic, and hypernatremic recognition and management. *Pediatr Rev*. 2015;36(7):274–285.

Table 80.5. Treatment With Oral Rehydration Therapy

Degree	*Dehydration ORT (Given Over 3–4 hours)*	*Replacement of Losses*	*Dietary Therapy*
Mild (5%) (≥13 years = 3%)	50 mL/kg of ORS	10 mL/kg for each diarrheal stool 5 mL/kg for each vomitus	Return to formula or milk as soon as vomiting resolves. Children who eat solid food can continue their regular diet.
Moderate (10%) (≥13 years = 6%)	100 mL/kg of ORS	10 mL/kg for each diarrheal stool 5 mL/kg for each vomitus	Return to formula or milk as soon as vomiting resolves. Children who eat solid food can continue their regular diet.

Abbreviations: ORS, oral rehydration solution; ORT, oral rehydration therapy.

most children with mild dehydration can be rehydrated relatively quickly and, in response to thirst, are likely to request the amount of fluid they need. Therefore, a simplified method of determining ORT fluid requirements has been developed (Table 80.5). This quantity of fluid is given over a period of 3 to 4 hours. In the child with ongoing losses, these losses should be replaced as well. Typically, it is not necessary to calculate the quantity of electrolytes that should be provided because these solutions are designed to adequately replace electrolytes in the otherwise healthy child who is dehydrated.

The parent or guardian should receive guidance about the volume (converted into common household measures [eg, 5 mL = 1 teaspoon and 15 mL = 1 tablespoon of water or ORS]) as well as the frequency and duration of ORT to be given at home. Small volumes of 5 to 15 mL administered with a syringe or teaspoon every 2 to 5 minutes are much more likely to be retained by the child who vomits larger volumes. Although this technique is labor intensive, it can be done by the parent or guardian and can deliver 150 to 300 mL/hour. As dehydration is corrected, vomiting often decreases and the child subsequently can tolerate larger volumes. With ORT, the frequency and amount of passing stool often increases during the initial period of treatment. The parent or guardian should be made aware that the primary purpose of ORT is to rehydrate the child, not to stop diarrhea, and that diarrhea will gradually decrease spontaneously. "Gut rest" (limiting oral intake) is not appropriate in most cases, and early refeeding with a return to the usual formula or milk and solids, if appropriate, should be prioritized.

Prognosis

The child with mild or moderate dehydration resulting from a self-limited childhood illness is likely to recover completely when given timely and appropriate rehydration therapy. It is more difficult to predict the prognosis of the child with severe dehydration or significant aberration in electrolyte balance. If managed appropriately, most such children also completely recover; however, despite closely monitored care, some children may experience permanent sequelae or poor outcomes.

CASE RESOLUTION

The child has moderate dehydration. Based on clinical assessment and weight change since the boy's last clinic visit, he is approximately 10% dehydrated. He does not show evidence of shock. His laboratory studies show a sodium level of 140 mEq/L, potassium of 3.7 mEq/L, chloride of 112 mEq/L, bicarbonate of 13 mEq/L, blood urea nitrogen of 13 mg/dL, and creatinine of 0.4 mg/dL. His renal status is likely to be adequate because he is urinating, and blood urea nitrogen and creatinine are normal for the patient's age. The child's serum sodium is 140 mEq/L, which is in the isotonic range. The serum potassium is 3.7 mEq/L, which is within normal range; however, this level may not accurately reflect this patient's total body potassium status. The level may decrease substantially as he is rehydrated and acidosis is corrected, indicating total body potassium depletion. His serum bicarbonate is 13 mEq/L, and his anion gap is 15 [140 – (112 + 13)], which is mildly increased and likely related to ketosis or mild lactic acidosis.

The calculation of this child's fluid and electrolyte needs is as follows, keeping in mind that his pre-illness weight was 12 kg:

Maintenance

Fluid requirement: 1,000 mL for first 10 kg + 100 mL for next 2 kg = 1,100 mL.

Deficit

Fluid replacement: 10% of the child's weight has been lost during this episode of dehydration = 1,200 mL deficit.

Ongoing Losses

Additional Fluid: Estimate this child's ongoing losses at 10 mL/kg for each stool. He had 1 loose stool while in the office, so 120 mL of additional fluid is added.

Sodium: The sodium content of diarrhea is variable; however, it is usually replaced with 0.9% NS.

Total fluid needs: 1,100 mL (maintenance) + 1,200 mL (deficit) + 120 mL (ongoing losses) = 2,420 mL/24 hours.

Electrolyte Needs

Sodium: 0.9% NS is used based on current recommendation.

Potassium: Estimate the child's maintenance and replacement needs to be 20 mEq K^+/1,000 mL fluid provided; this estimate can be modified based on follow-up laboratory values, if necessary.

Treatment

In the initial phase of therapy, provide NS 40 mL/kg per hour for approximately 2 hours. During this period, the patient's heart rate normalizes and he urinates. The initial parenteral phase provides 480 mL fluid as NS (0.9% NaCl). This amount of fluid is subtracted from the patient's total fluid needs. The remaining amount to be provided is 1,940 mL fluid. It is not necessary to prepare a special IV solution; 5% dextrose in 0.9% NS with 20 mEq/L KCl to run at 80 mL per hour is appropriate. As his GI symptoms improve, IV therapy is discontinued and ORT is instituted. The patient tolerates the ORT well and is discharged home.

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CHAPTER 81

Acute Kidney Injury

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CASE STUDY

A 10-month-old girl has a 2-day history of fever, vomiting, and watery diarrhea. The child has previously been healthy. Her diet has consisted of infant formula fortified with iron, baby food, and some table food. Since the onset of her illness, she has not been drinking or eating well, and she has thrown up most of what she has eaten. Her mother has tried to give her oral electrolyte solution and apple juice on several occasions but has had limited success. The child has had 8 to 10 watery stools without blood or mucus each day. Her temperature has varied between 37.0°C (98.6°F) and 38.8°C (101.8°F); the mother has given her daughter acetaminophen, which she has vomited up. The girl's 4-year-old brother and her parents are doing well and have no vomiting or diarrhea.

The physical examination reveals a severely dehydrated (estimated amount 15%), listless infant. Her weight is 9.4 kg (20.7 lb), her height is 74 cm (29.1 in), her temperature is 38.4°C (101.1°F), her heart rate is 168 beats per minute, her respiratory rate is 30 breaths per minute, and her blood pressure is 72/40 mm Hg with an appropriately sized cuff. Capillary refill is 2 to 3 seconds. The skin appears dry, but no rash is present. Head and neck, chest, heart, and abdominal examinations are normal. Pending the results of her blood studies, an intravenous fluid bolus of 180 mL normal saline (20 mL/kg) over 20 to 30 minutes is administered. This is followed by 2 more boluses of 180 mL normal saline each. The girl is catheterized to obtain urine and determine the urine flow rate over the next several hours. A urinalysis is performed.

Questions

1. What are the 3 stages of acute kidney injury?
2. What is the etiology of acute kidney injury?
3. How would the physician assess a patient with acute kidney injury?
4. How would the physician manage a child with acute kidney injury?
5. What are the indications for renal replacement therapy?

Acute kidney injury (AKI) is encountered in outpatient and inpatient settings and is associated with a high rate of morbidity and mortality depending on the primary cause of the insult. *Acute kidney injury* is defined as a sudden decrease in kidney function, signified by the accumulation of nitrogenous waste products (ie, blood urea nitrogen [BUN] and various other metabolic waste products) and impaired balance of fluid and electrolytes. With a better understanding of the pathophysiology of acute deterioration in renal function, the term AKI delineates the process of renal injury and encompasses the full spectrum of renal dysfunction, from early, mild renal injury with only a small elevation in serum creatinine level, to severe kidney injury requiring renal replacement therapy (ie, dialysis) as a continuum.

To better delineate the progression of AKI, in 2004 the Acute Kidney Injury Network Acute Dialysis Quality Initiative workgroup set forth the RIFLE criteria, which is based on serum creatinine level and urine output. The acronym RIFLE defines 3 stages of progressively increasing severity of renal injury (risk, injury, and failure) followed by 2 outcomes variables (loss and end-stage renal disease). These criteria, proposed in 2004 and validated in 2012 by the Kidney Disease: Improving Global Outcomes (KDIEGO) AKI workgroup, modified RIFLE for the pediatric population (pRIFLE) and its clinical use has been shown to improve outcomes in children (Figure 81.1). This classification is based in part on declining urine output; however, some children experience *nonoliguric renal failure*, in which urine output may remain normal or even increase. Decline in urine output is an essential component of risk assessment when determining severity of AKI in the pediatric patient because of the known association between the duration of oliguria and increased mortality.

The pRIFLE criteria are not applicable to newborns during the first few days after birth, however, because they may exhibit physiological oliguria during the first 24 hours after birth and their serum creatinine level initially reflects maternal creatinine values. Therefore, the pRIFLE criteria were further modified for neonates based on findings from the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study, which set the baseline creatinine level as the lowest level based on gestational age and set the serum creatinine threshold for stage 3 AKI at greater than or equal to 2.5 mg/dL rather than greater than 4 mg/dL.

The pRIFLE classification is intended to emphasize the reversible nature of the renal insult, which often is present in critically ill children admitted to pediatric or neonatal intensive care units (ICUs). It is anticipated that this precise and universal definition of AKI likely will enable physicians to rapidly recognize at-risk individuals and intervene promptly to improve immediate and long-term outcomes. The major limitation to the use of this classification is that it is not validated in children who present with AKI in an outpatient setting, whose etiology and outcomes often are dissimilar to those of inpatient, acutely ill children.

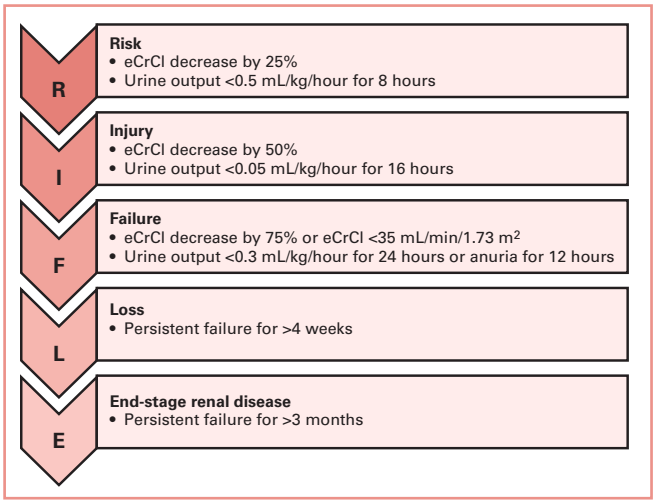

Figure 81.1. Pediatric risk for renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal disease (pRIFLE) criteria to assess the stage of renal injury.

Abbreviations: eCrCl, estimated creatinine clearance.

Derived from Bellomo R, Ronco C, Kellum JA , Mehta RL, Palevsky P; ADQI Workgroup. Acute renal failure--definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8(4):R204–R212 PMID: 15312219 https://doi.org/10.1186/cc2872.

Epidemiology

Acute kidney injury occurs in children with a wide variety of medical or surgical conditions and especially in children who are critically ill. The exact incidence of AKI in children is unknown because it not plausible to capture all cases of AKI, particularly in children who present to outpatient settings. The prevalence of AKI varies depending on geographic and demographic factors, which are responsible for the etiology of AKI. In developed countries, AKI has been increasing over the past few decades because of the increasing number of cardiopulmonary bypass surgeries performed to manage congenital heart disease, an increase in the number of solid organ and bone marrow transplantations, and the use of newly discovered nephrotoxic agents to manage a variety of disorders. Acute kidney injury resulting from primary renal disease appears to be on the decline compared with AKI caused by other systemic illnesses or their treatments. Acute kidney injury is often observed in patients in the ICU with sepsis or major trauma with severe bleeding or in the postoperative period after major heart surgery. According to Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) data published in 2016, of 4,683 critically ill children, 26.9% developed AKI and 11.6% had severe AKI (stage 2 and 3). Approximate 5% to 10% of patients in neonatal ICUs develop AKI, and most commonly as the result of perinatal hypoxia and postnatal hypotension.

Clinical Presentation

Most children with AKI initially present with clinical findings of the primary condition that ultimately results in the renal problem. In the critically ill child, a small increase in serum creatinine may be the first indication of AKI. However, decreased urine output, edema, hematuria, and/or hypertension may be the early sign or signs specifically related to declining renal function (Box 81.1). Additionally, hyperkalemia with cardiac arrhythmia, hyperventilation resulting from acidosis, and nausea and vomiting resulting from uremia may occur with progression of renal failure.

Etiology and Pathophysiology

Because of the recent epidemiologic shift from renal to nonrenal causes as common etiologic factors, for every child the primary care physician as well as the neonatal and pediatric intensivist should perform a risk assessment using the pRIFLE criteria and take the necessary steps to prevent AKI before the kidneys sustain serious injury. Frequently, the cause is multifactorial, and ischemic-hypoxic injury and nephrotoxic insults are important contributors; the pathophysiology of hypoxic ischemic injury and nephrotoxic insults is described herein.

The causes of AKI are usually grouped into 3 categories: prerenal, postrenal, and intrinsic renal disorders (Box 81.2 and Figure 81.2). Although prerenal failure and acute tubular necrosis (ie, intrinsic renal failure) may in fact be on opposite ends of a continuum, rather than separate entities, this classification system still aids in the conceptualization of the underlying problem and formulation of the initial treatment plan. Correspondingly, without timely intervention postrenal failure has the potential to cause renal damage and ultimately can result in intrinsic renal failure.

Prerenal Disorders

Prerenal disorders are the most common cause of AKI in pediatric patients and result in a decrease in total or effective circulating blood volume. An absolute decrease in circulating volume can be caused by blood loss from acute hemorrhage secondary to trauma or fluid loss and dehydration secondary to gastroenteritis. Heart failure or redistribution of body fluids (ie, third spacing) can result in decreased effective circulating volume. In each of these situations, the resulting decrease in the glomerular filtration rate (GFR) can be readily reversed by improving renal perfusion in its early stages. If hypoperfusion is prolonged, however, ischemic damage to the kidney occurs and intrinsic renal failure occurs.

Postrenal Disorders

In infancy and early childhood, urinary obstruction caused by posterior or anterior urethral valves or other congenital lesions involving the urinary tract can result in AKI. In the older child, kidney

Box 81.1. Diagnosis of Acute Kidney Injury

- Decreased urine output
- Hypertension
- Hematuria
- Edema
- Elevated serum creatinine level
- Blood urea nitrogen-creatinine ratio <20
- Elevated fractional excretion of sodium

Box 81.2. Etiology of Acute Kidney Injury in Children

Prerenal Disorders

- Decreased plasma volume
- Dehydration
- Hemorrhage
- Third spacing of plasma volume in the setting of burns, sepsis, bowel obstruction
- Other causes of renal hypoperfusion
- Shock
- Hypoxia
- Congestive heart failure
- Hepatorenal syndrome
- Bilateral renal artery stenosis
- Cardiac surgery

Postrenal Disorders

- Bilateral ureteropelvic or ureterovesical junction obstruction
- Posterior urethral valves
- Trauma to urethra
- Urethral stricture
- Neurogenic bladder
- Obstruction caused by kidney stone at the bladder neck or stone obstruction of both urinary tracts

Intrinsic Renal Disorders

- Vascular: renal artery or vein thrombosis, disseminated intravascular coagulation.
- Glomerular: hemolytic uremic syndrome, severe (ie, rapidly progressive) glomerulonephritis from any etiology.
- Interstitial: interstitial nephritis resulting from allergic reaction to drugs (eg, nonsteroidal anti-inflammatory drugs, oxacillin, methicillin), sepsis.
- Tubular (acute tubular necrosis): sepsis, postcardiac surgery, ischemia resulting from prolonged hypoperfusion; all causes listed in prerenal category, if sufficiently prolonged, may lead to acute tubular necrosis.
- Nephrotoxins: aminoglycoside antibiotics, indomethacin, radiocontrast agents, ethylene glycol, methanol, heavy metals.
- Pigments: myoglobinuria, hemoglobinuria.
- Uric acid: hyperuricemia, tumor lysis syndrome.
- Congenital renal anomalies (especially in newborns and young infants).
- Bilateral cystic dysplastic kidneys, reflux nephropathy, polycystic kidneys, oligomeganephronia.

stones, pelvic trauma, or complications following pelvic surgery are possible causes of postrenal failure.

Intrinsic Disorders

Intrinsic renal failure occurs because of injury to the vascular, glomerular, interstitial, or tubular components of the kidney (see Box 81.2). Intrinsic AKI can result from infection, ischemia, sepsis, or toxins. Acute kidney injury resulting from renal tubular lesions is called *acute tubular necrosis* (ATN). Histologic changes that characterize ATN include loss of brush border microvilli in tubular

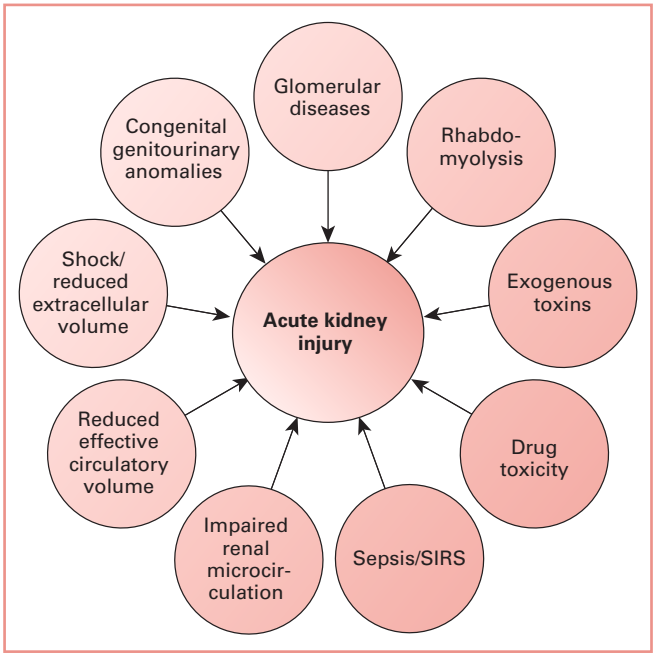

Figure 81.2. Common causes of acute kidney injury in children.
Abbreviation: SIRS, systemic inflammatory response syndrome.

cells, detachment of epithelial cells from basement membrane, and cast formation from cellular debris and protein.

The child with prolonged shock that manifests postcardiac surgery or that is caused by sepsis, trauma (ie, hemorrhage), or dehydration often develops ATN if effective circulating volume is not reestablished. This is the most frequent type of intrinsic AKI observed in children. Nonsteroidal anti-inflammatory drugs are increasingly being recognized as a cause of AKI in children, especially when used in patients with volume depletion. In the newborn or young infant, AKI may be superimposed on existing chronic congenital renal disease. In neonates, the prevalence of AKI ranges from 8% to 24% and is higher in neonates with severe asphyxia than in those with moderate asphyxia.

The pathogenesis of ATN in humans is controversial, and no single mechanism completely explains the sequence of events that results in ATN. Ischemic and toxic ATN result from a complex interplay of hemodynamic, vascular, and tubulointerstitial changes, including decreased blood flow to glomerular and tubular capillaries, resulting in reduced GFR; injury to cortical and medullary tubules with their cellular debris, resulting in tubular obstruction; and "back leak" of solute and water from the lumen to the interstitium, with further reduction in GFR. Increased production of endothelin and reduced production of nitrous oxide in the microvascular smooth muscle cells result in increased vasoconstriction and reduced perfusion, thereby perpetuating the renal injury. Renal tubular cells respond to the injury in many different ways, including no or minimal damage, sublethal injury, apoptosis, and necrosis. In the tubules, at the cellular level decreased oxygen delivery results in decreased production of adenosine triphosphate, which causes damage to cell membranes and cell cytoskeletons. Cell damage alters cell polarity, thereby promoting entry of increased amounts

of calcium into cells and increased intracellular free-radical formation. This in turn results in altered cell function, cell swelling, and apoptosis and cell death.

Certain intrinsic proteins also influence the onset of AKI, however. Low serum levels of bone morphogenetic protein 7, which is an antifibrotic, anti-inflammatory, and antiapoptotic factor that belongs to the transforming growth factor-β superfamily of ligands, is thought to play a role in the pathogenesis of postcardiac surgery–associated AKI. Acute kidney injury occurs more commonly in very low-birth-weight neonates carrying the heat shock protein 72 (1267) GG genetic variation, which is associated with low inducibility of heat shock protein 72, which itself plays an important role in ischemic renal injury. This suggests that some neonates are more susceptible to ischemic injury than others. It is hoped that with better understanding of the pathophysiology of AKI it will be possible to develop innovative, improved means of preventing, diagnosing, and managing the disease.

Differential Diagnosis

The diagnosis of AKI is established by the demonstration of a sudden increase in serum creatinine or BUN level. Decreased urine output is another helpful diagnostic factor. Identification of the clinical disorder that resulted in AKI is sometimes obvious, but at other times extensive evaluation may be necessary to discover the etiology of the primary disorder. It is also necessary to determine whether the child has chronic kidney disease or is experiencing superimposition of AKI on a preexisting renal condition (see Figure 81.2).

Evaluation

Acute kidney injury in children is among the few conditions for which laboratory and radiologic tests are often more helpful diagnostically than the history and physical examination.

History

The possibility for AKI should be anticipated in every child who is critically ill. A history of decreasing urine output, hematuria, dysuria, nausea, and vomiting should be sought in all patients. Prenatal and birth history may help identify the cause of AKI, such as oligomeganephronia in the child who was small for gestational age at birth or another complication that would have resulted in AKI. The presence of previous genitourinary disorders, delayed growth, and anemia may point to preexisting kidney conditions (Box 81.3). Family history of renal disorders can also aid in the differential diagnosis.

Physical Examination

An evaluation of physical growth, hypotension or hypertension, arrhythmia, dehydration, and edema should be made. Examination of the flank area for renal enlargement or tenderness and of the bladder for distention is necessary to help determine the etiology of AKI.

Laboratory Tests

Many biomarkers have been investigated for the early diagnosis of AKI in adults and children. The hope is that biomarkers found in the serum or urine will allow physicians to better detect early kidney injury, differentiate among multiple etiologies, and predict its severity. Many promising urinary biomarkers exist, including urinary or plasma neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, interleukin-18, liver-type fatty acid binding protein, markers of cell-cycle arrest (eg, tissue inhibitor of metalloproteinases-2), and insulin-like growth factor-binding protein 7, which have been identified to correlate with AKI to variable degrees. Both neutrophil gelatinase-associated lipocalin and tissue inhibitor of metalloproteinases-1 have been shown to correlate significantly with AKI in children in ICUs with various types of predisposing conditions. Recently, consideration has been given to the potential for assessing multiple biomarkers to determine changes in kidneys during the early phase of AKI. Studies analyzing the value of this tool are ongoing. In parallel, ongoing studies are assessing the value of screening programs, such as Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) and renal angina index, as a simplified alternative to already existing biomarkers. It is anticipated that in future this information will help physicians recognize at-risk individuals and intervene early to prevent progressive and permanent renal injuries.

Box 81.4 shows a list of laboratory tests recommended in all children with established or suspected AKI. If the child is not voiding frequently, temporary catheterization of the bladder is advisable (4–6 hours) to obtain urine for analysis. Residual volume should also be assessed, and the urinary flow rate (especially the response to initial fluid therapy) and presence of an outflow obstruction should

Box 81.3. What to Ask

Acute Kidney Injury

- How frequently is the child passing urine?
- Is the amount of daily urine decreased, increased, or unchanged?
- Does the child have hematuria or dysuria?
- Does the child have nausea or vomiting?
- Has the child had any previous urinary problems?
- For the older child: Does the child have a history of enuresis or nocturia?
- Is the child's physical development normal or delayed?
- Does the child have a history consistent with a primary condition that may have resulted in the acute renal failure/acute kidney injury?

Box 81.4. Laboratory Tests Recommended for Children with Established or Suspected Acute Kidney Injury

- Serum sodium, potassium, and bicarbonate levels
- Blood urea nitrogen level
- Creatinine, uric acid, calcium, and phosphorus levels
- Glucose level
- Total protein and albumin serum concentration
- Urinalysis and urine culture (if indicated)
- Spot urinary sodium and creatinine concentration and osmolality

be determined. All children with AKI and evidence of hyperkalemia should undergo electrocardiography (ECG).

Diagnosis of AKI can easily be established by laboratory tests and determination of urinary output over a specific time. *Oliguria* is defined as urine output less than 400 mL/m^2 per day or less than 1 mL/kg per hour in infants 1 year and younger, less than 0.75 mL/kg per hour in the child age 2 to 6 years, and less than 0.5 mL/kg per hour in children older than 6 years. Urinalysis, urine-specific gravity or osmolality, urine-plasma creatinine ratio, urinary sodium concentration, and fractional excretion of sodium help differentiate prerenal from intrinsic AKI (Table 81.1). Although a BUN-creatinine ratio of greater than 20:1 is suggestive of prerenal azotemia in adults, this is not necessarily true in infants and young children because they often normally have a BUN-creatinine ratio equal to or greater than 20.

Tubular epithelial cells and brown-pigmented casts are common in patients with ATN. Evidence of hematuria or proteinuria signifies glomerular disease, especially glomerulonephritis. The presence of blood on urine dipstick but absence of red blood cells (RBCs) on sediment examination is suggestive of hemoglobinuria (eg, hemolytic uremic syndrome) or myoglobinuria (eg, rhabdomyolysis) as the basis of ATN.

Although urinary indices are helpful in differentiating prerenal from intrinsic AKI, a simple clinical method can be used to distinguish between them. A therapeutic trial of volume expansion with 20 mL/kg of normal saline is administered intravenously over 30 to 60 minutes after first excluding the possibility of congestive heart failure or urinary obstruction. If oliguria persists at the end of 1 hour, furosemide (2 mg/kg) can be administered. If urinary output does not increase after furosemide administration, repeat administration of high-dose furosemide has few benefits and can cause toxicity, especially hearing loss, particularly in the preterm newborn, and should be avoided. Failure to respond to fluid and diuretic therapy is suggestive of intrinsic AKI.

Table 81.1. Diagnostic Indices in Acute Kidney Injury[a]

Test	*Prerenal Disorder*	*Intrinsic Renal Disorder*
Urinalysis	Normal, occasional granular casts	Renal epithelial cells; pigment casts
Urine osmolality (mOsm/kg H_2O)	>600	<400
Urine specific gravity	>1.020	<1.015
Urine sodium (mEq/L)	<15	>40
U-P creatinine	>40	<20
Fractional excretion of sodium (FE_{Na})[b]	<1%	>2%

Abbreviation: U-P creatinine, urine-creatinine (mg/dL) to plasma creatinine (mg/dL).

[a] Values in patients with nonoliguric acute kidney injury often overlap and fall between prerenal and renal values. Additionally, values in newborns differ from those in children older than 1 year.

[b] $FE_{Na} = (U_{Na}/U_{Cr}) \times (P_{Cr}/P_{Na}) \times 100$. U_{Na}, urinary concentration of sodium (mEq/L); FE_{Na}, fractional excretion of sodium; U_{Cr}, urinary concentration of creatinine (mg/dL); P_{Cr}, plasma concentration of creatinine (mg/dL); P_{Na}, plasma concentration of sodium (mEq/L).

Imaging Studies

Renal ultrasonography is the most useful test for differentiating postrenal from other forms of AKI. Renal ultrasonography can detect the presence or absence of kidneys, enlarged kidneys, dilated pyelocalyceal system, distended bladder, and other congenital anomalies. Other investigative tests, such as voiding cystourethrography, renal scanning, angiography, computed tomography, magnetic resonance imaging, and renal biopsy, may occasionally be necessary but generally are not indicated in the child with AKI during the initial workup. If a glomerular cause is suspected based on laboratory findings or radiologic evaluation, a biopsy is an appropriate next step. Chest radiography may also be helpful in detecting cardiac enlargement or pulmonary edema caused by fluid overload.

Management

Prevention is better than cure, and because of exponential advancement in the area of biomarkers to predict AKI in the acutely ill child, preventive measures are already in place to overcome manifestation of AKI by early intervention. The most common etiology among all children who develop AKI is prerenal azotemia. This condition is corrected by reestablishing adequate circulating volume. Prevention is particularly important because no currently available treatment can induce rapid recovery of renal function in humans after the condition has progressed to intrinsic AKI. Although low-dose dopamine and furosemide often are used in the initial management of AKI, many studies have shown that these medications do not enhance recovery of renal function. Fenoldopam mesylate, a dopamine receptor agonist, has been used in critically ill, hemodynamically unstable patients with AKI to improve renal perfusion, with some benefit in select patients. Certain drugs, such as adenosine triphosphate-magnesium chloride, thyroxine, atrial natriuretic peptide, and insulinlike growth factors, have been used in experimental animal models and some human trials without much success. The goal of therapeutic management of intrinsic AKI is maintenance of normal body homeostasis while awaiting spontaneous improvement, because proximal tubules can undergo repair and regeneration after damage.

After dehydration is corrected, if urine output is still not established daily fluid intake should be limited to replacement of insensible water loss (approximately 30%–40% of daily recommended fluid intake for age), any urinary losses, and fluid losses from nonrenal sources (eg, nasogastric drainage). Hyperhydration should be avoided in the patient with AKI because of its association with a high mortality rate and increased morbidity from edema, congestive heart failure, hypertension, hyponatremia, encephalopathy, and seizures. Recent studies have shown that fluid overload in patients in an ICU setting who did not previously have AKI can induce AKI, and in patients with AKI fluid overload can contribute to increased morbidity and mortality.

Patients with complete anuria require no sodium intake. Sodium losses, however, should be replaced daily in patients with any urinary output. Preferably, the amount of sodium required is determined by measuring daily urinary sodium losses, which can vary by individual patient.

In the patient with suspected AKI, potassium intake from all sources should be restricted. Severe hyperkalemia can often be avoided early in the course of the disease with strict adherence to potassium restriction. The level of serum potassium as well as changes on ECG should be closely monitored. The patient with mild hyperkalemia may be treated with ion exchange resin; sodium polystyrene sulfonate (eg, Kayexalate, Resonium A) may be given orally every 4 to 6 hours or by retention enema every 1 to 2 hours. Sodium polystyrene sulfonate should be mixed in water; mixtures containing polysorbate should be avoided because they may cause bowel perforation. Moderate hyperkalemia can be managed with insulin and glucose infusions or β agonists, which will drive the potassium intracellularly. In the patient with changes on ECG suggestive of hyperkalemia, such as tall T waves or widened QRS complexes, calcium gluconate should be given to stabilize the myocardium. If serum potassium continues to rise or evidence exists of cardiac instability despite conservative treatment, dialysis should be initiated to reduce the total burden on body potassium. Hypocalcemia and hyperphosphatemia are common in patients with AKI, and no treatment is required to address small alterations in levels of calcium and phosphorus. For serum phosphate greater than 8 mg/dL, a phosphate binder (eg, calcium carbonate, calcium acetate) may be used if the child can take nothing by mouth. If serum calcium is less than 8 mg/dL, intravenous (IV) or oral calcium should be administered to prevent tetany. If oral calcium supplements are given, the child will require 1,25 (OH) vitamin D (calcitriol by mouth or IV calcitriol) to enhance gastrointestinal absorption of calcium.

Mild metabolic acidosis is common in AKI and requires no treatment. If blood pH is less than 7.2 or serum bicarbonate is less than 12 mEq/L, sodium bicarbonate can be initiated and continued until renal function improves.

Adequate nutrition is important in the patient with AKI because it prevents excessive tissue breakdown. If renal failure is expected to be short in duration (3–4 days), most calories may be provided as carbohydrates. If AKI is expected to last longer, adequate calories in the form of carbohydrates along with daily protein intake of 1 g/kg should be provided.

Anemia should be identified and corrected if hemoglobin is less than 10 g/dL to improve oxygen and nutrient delivery to the tubules to facilitate regeneration of cells and establish their function. This can be achieved by maintaining an optimal hemoglobin level by transfusing packed RBCs and initiating subcutaneous or IV administration of epoetin alfa (eg, Procrit, Epogen) if renal failure is prolonged.

Many children with AKI can be managed by the conservative measures described previously. If renal failure lasts more than a few days or if complications arise, however, dialysis should be planned. The usual indications for dialysis include uncontrollable hyperkalemia or acidosis, volume overload with pulmonary edema or congestive heart failure unresponsive to diuretic treatment, progressive uremia with BUN level greater than 100 mg/dL, or creatinine clearance less than 15 mL/min/1.73 m^2. In preterm and term neonates, peritoneal dialysis is usually preferred over hemodialysis to avoid the major hemodynamic instability that often occurs with hemodialysis. In the critically ill child with overwhelming sepsis or multisystem organ dysfunction, however, early continuous venovenous hemodiafiltration is indicated for more gradual fluid removal, thereby avoiding significant fluctuations in the fluid balance and optimizing nutritional support.

Acute renal injury often can be prevented by anticipating its possible occurrence in the child with a high-risk condition, such as dehydration, trauma, sepsis, and shock, or after cardiac surgery. Prompt recognition of prerenal failure and aggressive management of it with volume expansion may prevent the manifestation of intrinsic AKI. Nephrotoxic agents, such as gentamicin, should be avoided in the high-risk patient if possible. When these drugs are used, they should be monitored meticulously, with frequent measurement of blood levels.

Prognosis

The in-hospital and long-term complications in the child with AKI can be associated with poor cardiovascular and renal prognosis. Three scenarios exist in which a child with AKI can develop chronic kidney disease. First, the initial episode of AKI may cause permanent damage to the kidneys, resulting in end-stage renal disease. Second, recovery from the initial episode may be incomplete, resulting in relatively low renal function compared with baseline function, and consequently, chronic kidney disease. Third, the child who regains near-normal or normal renal function continues to be at increased risk for developing kidney failure years later compared with the child who did not have AKI.

The duration of oliguria in AKI may be short (1–2 days) or long (a few weeks). Typically, recovery is first indicated by an increase in urinary output. Blood urea nitrogen and creatinine levels may rise during the first few days of diuresis before beginning to return to normal. During diuresis, large quantities of sodium and potassium may be lost in the urine. Serum electrolyte levels should be closely monitored, and adequate replacements should be made to prevent hyponatremia and hypokalemia.

In the child with AKI, outcomes mainly depend on the primary condition, severity of damage to other organs, and physician expertise in managing AKI. Nonoliguric AKI is consistently associated with a shorter clinical course and better prognosis than oliguric AKI. Most children with ATN recover completely. However, children with more severe kidney involvement (eg, cortical necrosis) may have residual renal impairment or chronic renal failure, and children who are critically ill have a 60% mortality rate. Studies on older children have also shown that AKI results in chronic kidney disease in a higher percentage of children than was previously appreciated.

Early recognition of potential risk factors and prompt intervention will reduce long-term sequelae of AKI, particularly the development of end-stage renal disease in the long term.

CASE RESOLUTION

A series of diagnostic studies is performed. The laboratory results are hemoglobin, 13.8 g/dL; hematocrit, 41%; white blood cell count, 12,400/mcL; neutrophils, 58%; band forms, 6%; lymphocytes, 32%; monocytes, 3%; and eosinophils, 1%. The platelet count is 277,500 platelets/mcL. Serum sodium is 136 mEq/L; potassium, 5.1 mEq/L; chloride, 110 mEq/L; bicarbonate, 10 mEq/L; BUN, 84 mg/dL; creatinine, 2.8 mg/dL; and glucose, 68 mg/dL. The urinalysis reveals a specific gravity of 1.015; trace protein, blood, white blood cell, and nitrite are all negative; and the sediment has many epithelial cells, 1 to 2 RBCs, and many granular and pigmented casts. Spot urinary sodium is 65 mEq/L, creatinine is 39 mg/dL, and fractional excretion of sodium is 3.4%.

These results, particularly the increased fractional excretion of sodium, are most consistent with a diagnosis of intrinsic AKI. The history points to prerenal failure initially, after which prolonged hypovolemia contributed to ischemia of the kidneys, resulting in intrinsic renal failure. According to the pRIFLE criteria, the laboratory results indicate that the patient is likely in stage 3 failure. Recovery may take a few days to a few weeks. The patient is admitted to the pediatric step-down unit, where fluids are adjusted according to her urine output and electrolytes are monitored frequently.

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CHAPTER 82

Ingestions: Diagnosis and Management

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CASE STUDY

A 2-year-old girl is found by her mother with an open bottle of pills and pill fragments in her hands and mouth. She is rushed to the emergency department. She is sleepy but able to be aroused. The vital signs are temperature of 37.1°C (98.8°F), heart rate of 120 beats per minute, respiratory rate of 12 breaths per minute, and blood pressure of 85/42 mm Hg. The pupils are 2 mm and reactive. Skin color, temperature, and moisture are normal. She has no other medical problems.

Questions

1. What history questions should be asked to help identify the substance ingested?
2. What physical examination findings can offer clues to the substance ingested and the seriousness of the ingestion?
3. What other diagnostic tests might be helpful in treating ingestion patients?
4. What are the management priorities?

Ingestions are a common problem presenting to pediatric practitioners. Three scenarios frequently encountered are accidental ingestions by preschool-age children, intentional suicide attempts by adolescents, and recreational drug use. This chapter discusses the general approach to the child who has ingested a potentially poisonous substance. Ingestions of specific substances are beyond the scope of this chapter, as is toxicity occurring by dermal, ophthalmologic, and inhalational routes. The general approach to the history, physical examination, laboratory tests and diagnostic studies, and management, especially decontamination, is useful for all ingestions, however.

Epidemiology

Most calls made to poison control centers involve pediatric patients. Poison control center data from 2016 show that pediatric patients younger than 20 years accounted for 60% of exposures and young children aged 0 to 5 years accounted for 46%. Among younger children boys were more commonly exposed, whereas girls predominated in adolescence. For children aged 0 to 12 years 3.5% of exposures are intentional, whereas for adolescents aged 13 to 19 years 27% are intentional, and for adults 69% are intentional.

The most common substances ingested overall are analgesics, including acetaminophen, nonsteroidal anti-inflammatory drugs, and narcotics; household cleaning substances; and cosmetics/personal care products. The most common fatal ingestion in children is analgesics (often narcotics that are not their own prescription). Other common pediatric fatal poisonings are stimulants and street drugs, carbon monoxide poisoning, antidepressants, and disc battery ingestions. A registry that included cases on which a medical toxicologist was consulted (presumably for serious exposures) at 31 participating centers reported on the most common agents involved for infants and toddlers age 2 years and younger: 16% cardiac drugs, 15% psychotropic drugs, 9% recreational drugs and controlled narcotics, 9% analgesics, 7% cleaning products, 5% scorpion stings, and 4% toxic alcohols.

Fatalities are uncommon overall and are more likely to occur with intentional ingestion by older children. Poison control center data from 2016 revealed 31 pediatric fatalities (age 0–12 years) and 42 adolescent fatalities (age 13–19 years). Children accounted for 2% of total toxicologic fatalities for the year, whereas adolescents accounted for 3% and adults for the remainder. Young children tend to ingest nontoxic substances or small quantities of toxic substances. Review of trends over the past few years indicates a reduction in overall calls but an increase in calls about serious exposures. Fatality rates have remained stable.

The frequency of exposures to analgesics (narcotics), cardiac drugs, and psychotropic drugs in pediatric patients is linked to an overall rise in adult prescription drug use. Cough and cold medications are an increasingly recognized source of toxicity in young children, and the US Food and Drug Administration recommends against their use in children younger than 6 years. Another new source of serious toxic exposures in children is laundry and dishwasher detergent capsules, which can have an appearance similar to candy. A rise in inadvertent pediatric marijuana exposures has been reported in states with legalized marijuana, with edible sources playing a sizeable role.

Recreational drug use is another source of serious exposures in adolescents. Narcotics, cocaine, amphetamines, and ecstasy remain popular, and newer forms of recreational drugs include energy drinks with or without alcohol, synthetic cathinones ("bath salts"), synthetic cannabinoids ("K2," "Spice"), dextromethorphan, inhalants (especially computer cleaners), and the hallucinogenic herb salvia, which is legal in many states and also has opioid effects. Contamination of street drugs with high-potency opiates, such as carfentanil, is contributing to the rise in opioid fatalities.

Clinical Presentation

The clinical presentation following an ingestion varies considerably depending on the substance ingested. Some patients may not present with a clear history of a toxic ingestion. The physician must maintain a high index of suspicion for poisoning as the cause of symptoms such as altered behavior, depressed level of consciousness, cardiac dysrhythmia, vomiting, seizure, and autonomic changes.

Pathophysiology

The pathophysiologic profile depends on the substance. Some toxins act on a particular organ system (eg, acetaminophen on the liver, ethanol on the central nervous system), whereas others act diffusely at the cellular level (eg, cyanide). Generally, drugs are absorbed, distributed within the body, metabolized, and excreted. Drug levels obtained prior to completion of absorption and distribution may not reflect the peak level. Interventions focus on preventing absorption, sometimes on preventing metabolism into a more toxic by-product, and on enhancing excretion. Toxic effects may be delayed or prolonged when an extended-release form of a drug has been ingested, with drugs likely to form concretions (eg, iron, aspirin, theophylline), or when toxicity results from an active metabolite (eg, toxic alcohols, acetaminophen, acetonitrile, dapsone). Pharmacogenetics are increasingly recognized as having an important role in individual responses to medications and toxins. Genetic variations in enzymatic activity in drug metabolism may result in toxicity through excessively rapid metabolism of a drug to its active metabolite, or through slow metabolism of a drug to its inactive metabolite. For example, a cytochrome P-450 CYP2D6 genotype has been linked to rapid metabolism of codeine to active morphine, resulting in toxicity and even fatality. The US Food and Drug Administration has added a boxed warning on codeine and a contraindication for its use after tonsillectomy or adenoidectomy in children.

Differential Diagnosis

The differential diagnosis of toxic ingestions is broad. For the patient with a history of ingestion, the differential diagnosis is narrowed to substances available to the child. If no history of ingestion is given, the physician should include ingestion in the differential diagnosis when evaluating symptoms and signs such as altered mental status, altered behavior, metabolic derangement, cardiac dysrhythmia, hypotension and shock states, seizure, respiratory distress or apnea, cyanosis, vomiting, and diarrhea (Box 82.1). In fact, almost any symptom complex may result from a toxic ingestion.

Box 82.1. Symptoms of Toxic Ingestion

- Bradycardia or tachycardia
- Hypothermia or hyperthermia
- Respiratory depression or hyperpnea
- Hypotension or hypertension
- Mydriasis or miosis
- Altered mental status or abnormal behavior
- Seizure
- Cardiac dysrhythmia
- Metabolic derangement
- Nausea, vomiting, diarrhea

Evaluation

A detailed history of what and how much the patient ingested is key to the evaluation. Physical examination should focus on identifying symptoms and serious complications. The patient should be monitored and reassessed frequently. Laboratory and other diagnostic studies can be tailored to the specific ingestion.

History

The most important questions address the ingestion (Box 82.2), such as, What did the patient ingest? What is the maximum possible amount that was ingested? When did the ingestion occur? What symptoms are occurring? History of previous medical conditions is also important to identify increased susceptibility to a particular toxin (eg, seizure disorder with ingestion of a substance that causes seizures); assess for factors that may have precipitated the ingestion, such as depression; and assess for medications that may interact with or exacerbate the toxic effects of the ingested substance (eg, acetaminophen ingestion in a patient taking a cytochrome P-450 inhibitor).

Parents and caregivers should be encouraged to bring in the container and any remains of the substance ingested. The physician should attempt to obtain the exact formulation because generic and brand name drugs may differ. The physician must also be aware of possible combination products. Investigative methods such as calling

Box 82.2. What to Ask

Toxic Ingestion

- What did the child take? (If unknown, what is available to the child?)
- How much did the child take? (If unknown, what is the maximum amount possible?)
- When did the child take it? (If unknown, how long was the child unattended or unobserved?)
- What symptoms have occurred, and when did the symptoms begin relative to the time of ingestion?
- What other medical conditions does the child have?
- What medications does the child take regularly?

or sending a family member to the home to identify the product, calling the pharmacy on a prescription label, or identifying a pill by comparing its picture and imprint to those in a pharmaceuticals reference may be necessary. Internet search engines may be used to search the imprint on a pill or identify foreign medications.

Caregivers should be questioned about all available drugs or other toxic substances in the household. Sometimes caregivers must be encouraged to mention all substances in the household, even those they do not think the child could possibly have obtained. The physician must also ask about medications used by recent visitors (eg, grandparents) and the possibility of an exposure at a recently visited household or location. It is important not to overlook herbal preparations, vitamins, alternative medications, household products (including cleaning and personal care products), gardening products, chemicals used in hobbies or work, and alcohol or illicit drugs belonging to an adult. Caregivers may initially overlook these as they concentrate only on recalling "medications." It may be helpful to interview siblings or friends of an adolescent suspected of recreational drug use. The physician must maintain a high index of suspicion for unreported co-ingestants, especially in adolescent suicide attempts.

Although often difficult, it is important to attempt to determine the quantity of drug that was available to the patient and how much is currently missing. It may be necessary to count pills or measure liquid to make the determination. For estimating liquids, the approximate volume of a swallow is 0.3 mL/kg. The physician should always assume the "worst case" (ie, the patient took all of the drug that is missing). History about the amount ingested may be inaccurate, especially when elicited from the adolescent with intentional ingestion.

The physician should attempt to determine approximately what time the ingestion occurred. Symptoms are usually expected within a defined time range. Recommended observation periods before discharge take into account expected symptoms based on the length of time since the ingestion. Timing may also be important in determining what substance was most likely ingested. For example, ingestion of mushrooms that cause a self-limited illness usually results in gastrointestinal (GI) upset within 4 to 6 hours, whereas *Amanita* mushrooms that may ultimately result in hepatic failure typically present with GI upset in 6 to 12 hours.

The physician should ask about current symptoms and when they started relative to the time of the ingestion. In a patient without a definite history of ingestion, certain *toxidromes* (ie, recognizable combinations of symptoms suggestive of a certain class of medications or toxins) may be suggestive of a specific substance or class of substances. Whether the patient is symptomatic and what symptoms are present may guide the workup for an unknown ingestion, determine whether hospitalization is necessary, or dictate therapy.

Physical Examination

If the substance ingested is known, the physical examination should be focused on identifying expected symptoms of toxicity. A general physical examination should always be performed, however, because co-ingestion of another undisclosed substance must be considered. Particular attention should be paid to all 4 vital signs (ie, temperature, respiratory rate, heart rate, blood pressure); pupillary size and reaction; breathing (eg, Kussmaul respiration that occurs with acidosis); mental status; distinctive breath odors; presence or absence of bowel sounds; and skin color, temperature, and moisture. The patient's weight should be measured, because toxicity is often estimated based on milligrams of drug ingested per kilogram of body weight. Because symptoms may develop or worsen if peak levels of the toxic substance have not been reached at the time of initial evaluation, continual reassessment and cardiorespiratory monitoring are imperative. If a symptomatic patient is noted to have a typical toxidrome, therapy may be initiated based on the toxidrome without confirmation of the exact substance ingested. Some common toxidromes and their treatments are listed in Table 82.1.

Laboratory Tests

Qualitative drug screening (reporting only the presence or absence of the drug) of urine or blood often is done when poisoning is part of a broader differential diagnosis for symptoms such as altered mental status or acute behavioral changes. Such drug screening is rarely helpful in the patient with acute poisoning because typically results are not rapidly reported, testing can be done for only a limited number of substances, and false-positive and -negative results may occur. Given the frequency of narcotic ingestions, it is important to note that synthetic opioids (eg, fentanyl, methadone, oxycodone, hydrocodone) are not detected by typical hospital immunoassay "tox screens." Laboratory tests and diagnostic studies to consider for the patient with known or suspected toxic ingestion are listed in Box 82.3.

Quantitative drug levels for specific drugs can be helpful to estimate severity of expected symptoms or to rule out ingestion of that drug, however. Examples include acetaminophen, salicylate, ethanol, methanol, ethylene glycol, iron, theophylline, lithium, anticonvulsants, and levels of carboxyhemoglobin or methemoglobin by blood gas analysis. With the exception of acetaminophen and ethanol, such levels should be measured only when suggested by the history or physical examination. Many toxicology experts feel that because acetaminophen overdose produces few acute symptoms, may lead to fulminant hepatic failure, and is readily treatable with an antidote, and because acetaminophen is a frequent ingredient in combination products, acetaminophen level should be determined for all patients with a history of ingestion. In adolescents and adults, ethanol is a common co-ingestant, and ethanol levels are routinely measured. Routine salicylate levels are likely to be low yield in the absence of suspicion based on history or physical examination, although some physicians do obtain them as well.

Serum chemistries and osmolarity may offer clues about what was ingested when the substance is unknown. The *anion gap* is calculated as $[Na] - ([Cl] + [HCO_3])$ and is normally 8 to 12 mEq/L. An elevated anion gap indicates the presence of metabolic acidosis and occurs in ingestions and conditions identified by the MUDPILES mnemonic: methanol, uremia, diabetic ketoacidosis, paraldehyde

Table 82.1. Toxidromes

Toxidrome	*Toxins/Drugs*	*Symptoms*	*Treatment*
Narcotic or opiate	Oxycodone, hydrocodone, methadone, fentanyl, heroin, codeine, morphine	Nausea/vomiting, respiratory depression, miosis, altered mental status, coma	Naloxone, respiratory support
Cholinergic (parasympathomimetic)	Organophosphate and carbamate pesticides	Diarrhea, urination, miosis, bronchorrhea and bronchospasm, emesis, lacrimation, lethargy, salivation (ie, DUMBELLS)	Atropine, pralidoxime (ie, 2-PAM)
Anticholinergic	Antihistamines, jimson weed, antipsychotic agents, some antidepressants, Parkinson medications	Flushing ("red as a beet"), dry skin and mucous membranes ("dry as a bone"), hyperthermia ("hot as a hare"), delirium ("mad as a hatter"), mydriasis ("blind as a bat"), tachycardia, urinary retention, ileus/decreased bowel sounds	Supportive care
Sympathomimetic	Cocaine, amphetamines, ephedrine	Mydriasis, anxiety, tachycardia, hypertension, hyperthermia, diaphoresis	Quiet environment, benzodiazepines
Sympatholytic	Clonidine, beta blocker (eg, propranolol)	Bradycardia, hypotension, miosis, possibly lethargy	Supportive care, fluids and pressors if necessary for hypotension, atropine for symptomatic bradycardia
Tricyclic antidepressant	Imipramine, amitriptyline[a]	Seizure, tachycardia, prolonged QRS complex, altered level of consciousness, cardiac dysrhythmia	Sodium bicarbonate
Salicylate	Aspirin, methyl salicylate, oil of wintergreen	Hyperventilation, nausea/vomiting, tinnitus, hyperthermia, metabolic acidosis	Alkalinization with sodium bicarbonate (ie, $NaHCO_3$; confirm salicylate level)
Serotonin syndrome	Selective serotonin reuptake inhibitors[a]	Altered mental status, neuromuscular rigidity, tremors, or hyperreflexia; autonomic instability: hyperthermia, mydriasis, tachycardia, hypertension or hypotension	Supportive care

[a] Not an exhaustive list.

Box 82.3. Laboratory Tests and Diagnostic Studies to Consider for Toxic Ingestion

- Specific drug levels as indicated
- Qualitative urine or blood toxicology screening
- Acetaminophen level; consider ethanol and salicylate levels
- Serum chemistries (ie, calculate serum anion gap)
- Serum osmolarity (ie, calculate osmolar gap)
- Liver function panel and renal function tests
- Rapid bedside glucose test
- Urine pregnancy test
- Pulse oximetry
- Electrocardiography
- Arterial blood gas with carbon monoxide and methemoglobin levels
- Urinalysis
- Creatinine phosphokinase level
- Chest radiography
- Abdominal radiography for radiopaque tablets

and phenformin, iron and isoniazid, lactic acidosis, ethylene glycol and ethanol, and salicylates and solvents (eg, toluene). The *osmolar gap* is the difference between the measured serum osmolarity and the calculated osmolarity (given by the formula 2[Na] + [glucose]/18 + [BUN]/2.8). The normal osmolar gap is less than 10 mOsm. An elevated osmolar gap occurs with ingestion of alcohols such as ethanol, methanol, ethylene glycol, and isopropanol.

Depending on the level of suspicion for acidosis, hypoxemia, or abnormal hemoglobins (ie, carboxyhemoglobin and methemoglobin), arterial blood gas analysis may be indicated. Because hypoglycemia may be noted with some ingestions and is easily treated, a rapid bedside glucose test should be done on all patients. Urinalysis and creatinine phosphokinase level tests may be performed to evaluate for signs of rhabdomyolysis if the patient is deemed at risk. All females of childbearing age should undergo a urine pregnancy test. Assessment of liver and renal function is often important because many substances are metabolized by these routes.

Diagnostic Studies

Pulse oximetry and cardiorespiratory monitoring should be instituted for all serious ingestions. Electrocardiography may be indicated if cardiac toxicity is expected. Other studies are tailored to the specific ingestion, such as endoscopy after ingestion of caustic acids or alkalis.

Imaging Studies

Specific imaging studies may be indicated for certain ingestions, such as chest radiography in the case of hydrocarbon ingestion to look for signs of aspiration. An abdominal radiograph may be helpful in identifying ingestion of radiopaque substances and monitoring the effectiveness of GI decontamination procedures for removing such substances. The mnemonic CHIPS can be used for remembering which medications are radiopaque: chloral hydrate, heavy metals, iron, phenothiazines, and slow-release (ie, enteric-coated) medications. In practice, abdominal radiography is primarily used in iron ingestion and suspected body-packing with illicit drugs.

Management

Management strategies are specific to the substance ingested. The regional poison control center should be consulted for advice on treatment and length of time to observe the asymptomatic patient. A single telephone number, 1-800-222-1222, automatically routes the caller to 1 of the appropriate 55 regional poison control centers in the United States. Generally, the approach to management includes attention to the basics of resuscitation (circulation, airway, breathing), decontamination methods, specific antidotes when available and indicated, and meticulous supportive care, often in an intensive care unit.

Decontamination

Decontamination techniques are used to prevent or minimize absorption of the toxic substance and to enhance its elimination. They are a critical part of the treatment of the acutely poisoned patient and should be used whenever a significant ingestion is suspected (Table 82.2).

Historically, ipecac syrup was commonly recommended for home use to induce vomiting in the event of an accidental ingestion. The American Academy of Pediatrics released a policy statement in 2003 stating that ipecac syrup should no longer be kept in homes and is not recommended because studies showed that its use resulted in no difference in outcomes. Gastric lavage, in which a large nasogastric tube is placed and the stomach is washed with normal saline theoretically removes toxic substance from the stomach, thereby preventing absorption. At best (ie, immediate performance after ingestion), however, less than one-third of gastric contents are removed by this method. Additionally, this technique may interfere with the use of activated charcoal, which usually is a more effective therapy. Gastric lavage is technically difficult to perform in young children because of the need to pass a large-bore tube. Gastric lavage also has a high rate of complications, such as aspiration and esophageal trauma. Gastric lavage is not recommended for routine use. The American Academy of Pediatrics released a policy statement in 2003 stating that ipecac syrup should no longer be kept in homes. Ipecac syrup was administered in 0.01% of pediatric ingestions in 2011.

Table 82.2. Summary of Gastric Decontamination Techniques

Technique	*Dose*	*Contraindications*
Gastric lavage	15 mL/kg aliquots normal saline to maximum of 400 mL until lavage fluid is clear (may be several liters)	ALOC with unprotected airway Caustics: acids and alkalis Hydrocarbons Expected ALOC >1 hour since ingestion
Activated charcoal	1–2 g/kg or <6 years: 25–50 g ≥6 years: 50–100 g	ALOC with unprotected airway Absent bowel sounds or bowel obstruction Substance not bound by charcoal
Cathartics	Magnesium citrate 4 mL/kg 70% sorbitol 1 g/kg	Not recommended for routine use Repeated doses can cause dehydration or electrolyte imbalances
Whole-bowel irrigation	Toddler and preschool age: polyethylene glycol solution 500 mL/hour 6–12 years: 1,000 mL/hour Adolescent and adult: 1.5–2 L/hour Continue until rectal effluent is clear	Bowel obstruction, ileus, perforation, or hemorrhage ALOC with unprotected airway
Lipid emulsion 20%	1.5 mL/kg initial bolus intravenous, then 0.25 mL/kg/minute for 30–60 minutes	For lipophilic drug overdose with severe cardiotoxicity

Abbreviation: ALOC, altered level of consciousness.

Activated charcoal is the mainstay in decontamination therapy of ingestion. Charcoal binds toxins, and because it is not absorbed in the GI tract, the charcoal-toxin complex passes through and is eliminated. Its efficacy decreases with increasing time since ingestion, and ideally it should be started within 1 hour of the ingestion. The optimal dose of charcoal is 10 times the amount of substance ingested. Because the exact amount of toxin ingested is often unknown, activated charcoal is usually dosed at 1 to 2 g/kg (teenagers and adults, 25–100 g). The amount of charcoal given is limited only by what the child can tolerate. Only a few substances are not absorbed by activated charcoal, and the mnemonic PHAILS can be used to remember them: pesticides; hydrocarbons and heavy metals; acids, alkalis, and alcohols; iron; lithium; and solvents. The main complication of charcoal administration is aspiration pneumonitis, which mainly occurs in patients with altered level of consciousness and an unprotected airway. If charcoal is not voluntarily taken by the child, it may be administered via nasogastric tube. Endotracheal intubation (preferably with a cuffed tube) to protect the airway first may be necessary in the patient with altered mental status, because charcoal aspiration can result in severe chemical pneumonitis. It is imperative that nasogastric tube placement in the GI tract (as opposed to the respiratory tract) be confirmed before charcoal administration.

Cathartics (most commonly sorbitol) have been used to decrease transit time and improve elimination of the toxin through the GI tract and to counteract activated charcoal-induced constipation. The cathartic is often mixed with the activated charcoal and may serve to improve the palatability of the charcoal. A significant benefit from cathartic use has never been demonstrated, however, and a risk of dehydration and electrolyte disturbances exists, particularly in young children. The American Academy of Clinical Toxicology recommends against use of cathartics. Under no circumstances should repeat doses of cathartics be administered.

Multiple-dose charcoal, which has been called "GI dialysis," may remove drugs from the bloodstream by promoting diffusion back into the GI tract and subsequent binding to charcoal. Activated charcoal at the same dose previously used is repeated approximately every 4 hours. Cathartics should not be mixed with the charcoal for repeat doses. Multiple-dose charcoal is useful for a small number of drugs, such as phenobarbital, theophylline, carbamazepine, dapsone, and quinine. It should be used only if a potentially life-threatening amount has been ingested. It should not be used for drugs that can cause an ileus (eg, tricyclic antidepressants).

Whole-bowel irrigation involves infusion of a solution usually used for cleansing of the bowel prior to GI surgery (eg, polyethylene glycol). It is especially useful for slow-release medications, for tablets that dissolve slowly and may cause concretions (eg, iron), and in ingestions for which charcoal is not likely to be effective (eg, heavy metals). A nasogastric tube is used to infuse the solution at a rate of 500 mL/hour in young children and 1 to 2 L/hour in older children and adolescents. Clear rectal effluent is the end point; a bedpan may be necessary. Whole-bowel irrigation should not be used in the setting of bowel obstruction, ileus, perforation, or hemorrhage or altered mental status with an unprotected airway.

Hemodialysis may be used for serious ingestions of ethylene glycol, methanol, phenobarbital, lithium, salicylate, or theophylline. Charcoal hemoperfusion, in which blood passes through a charcoal cartridge rather than a dialysis machine, is used rarely for severe theophylline poisoning. Urinary alkalinization (by administration of sodium bicarbonate) can increase elimination of weak acids by keeping the drug in its ionic state, thus preventing reabsorption in the renal tubule. It is used mainly for significant salicylate, phenobarbital, and isoniazid poisonings.

Lipid emulsion (eg, Intralipid) is becoming recognized as a potential treatment for lipophilic drug overdoses and has been used successfully for managing severe cardiotoxicity from bupivacaine hydrochloride, haloperidol, and verapamil hydrochloride overdoses. It is unclear by what method this agent works. Although ideal dosing and indications have not been established, 1 suggested treatment protocol to consider is 1.5 mL/kg of 20% lipid emulsion initial bolus, followed by 0.25 mL/kg per minute for 30 to 60 minutes. Boluses may be repeated in the setting of severe cardiotoxicity and dysrhythmias.

Supportive Care

Attention to the basics of resuscitation (circulation, airway, breathing) is always the first step in management. Hypoglycemia must be assessed and managed as soon as possible. Dextrose 0.5 to 1 g/kg intravenously is administered for hypoglycemia; glucagon may be used if dextrose cannot be given. Seizure generally is treatable with benzodiazepines. Glucose and electrolyte levels should be normalized. For the patient with seizure caused by isoniazid ingestion, pyridoxine is indicated. Shock requires aggressive fluid resuscitation. Fluid-resistant shock may require vasopressors, most commonly dopamine, epinephrine, or norepinephrine. Resistant shock in the setting of beta blocker ingestion may respond to glucagon, and in the setting of a calcium channel blocker ingestion to insulin plus glucose. Dysrhythmias generally should be managed by following pediatric advanced life support (PALS) protocols, although specific ingestions may respond to specific therapies. Sodium bicarbonate is the first-line treatment for dysrhythmias associated with ingestions of antihistamines, class 1 antiarrhythmic drugs (ie, lidocaine, quinidine, procainamide hydrochloride), cocaine, and tricyclic antidepressants. Beta blocker ingestions may respond to atropine and glucagon, whereas ingestions of calcium channel blockers are managed with calcium. Procainamide hydrochloride, which is found on PALS algorithms, should be avoided for patients with dysrhythmia resulting from overdoses of antihistamines, quinidine and other class 1 antiarrhythmic drugs, digoxin, quinine, and tricyclic antidepressants. Amiodarone hydrochloride, another agent found on PALS algorithms, should also be avoided in the management of antihistamine ingestions. Electrolyte imbalances should be assessed and corrected. Suicidal ideation should be assessed, often in conjunction with a mental health professional.

Antidotes

Antidotes or medications that counteract the pathophysiologic mechanisms of the toxin are available for only a few ingestions (Table 82.3). Important antidotes are N-acetylcysteine for acetaminophen, naloxone hydrochloride for narcotics, oxygen for carbon

Table 82.3. Select Antidotes for Specific Ingestions

Toxin	*Antidote*
Acetaminophen	N-acetylcysteine
Anticoagulants (warfarin-like)	Vitamin K
Anticholinergic	Physostigmine
Benzodiazepine	Flumazenil
Beta blocker	Glucagon
Calcium channel blocker	Calcium, insulin + glucose
Carbamate pesticide	Atropine
Carbon monoxide	Oxygen
Cyanide	Cyanide antidote kit
Digoxin	Digoxin immune Fab (ovine; Digibind)
Ethylene glycol	Fomepizole, ethanol
Iron	Deferoxamine
Isoniazid	Pyridoxine
Lead	Dimercaprol (ie, BAL), ethylenediaminetetraacetic acid, DMSA
Mercury	BAL, DMSA
Methanol	Fomepizole, ethanol
Methemoglobinemia	Methylene blue
Narcotics	Naloxone hydrochloride
Organophosphate pesticide	Atropine, pralidoxime (ie, 2-PAM)
Rattlesnake bite	Crotalidae polyvalent immune Fab (ovine; CroFab)
Sulfonylurea oral hypoglycemic	Dextrose, octreotide
Tricyclic antidepressant	Sodium bicarbonate

Abbreviations: BAL, British antilewisite; DMSA, dimercaptosuccinic acid.

monoxide poisoning, sodium bicarbonate for tricyclic antidepressant cardiotoxicity, digoxin immune fab (eg, Digibind, DigiFab) for digoxin, and deferoxamine for iron. Antidotes are not without adverse effects themselves and should be given only in cases of symptomatic or, as in the case of acetaminophen, potentially symptomatic ingestions of significant amounts. The poison control center staff can be quite helpful in guiding physicians in the use of antidotes.

Anticipatory Guidance and Prevention

Most ingestions are nontoxic and require only observation for a few hours. These episodes do, however, provide an excellent opportunity to discuss poisoning prevention with parents and caregivers. Possible toxins, including prescription and over-the-counter medications, cleaning and household products, cosmetics and nail care products, toxic plants, gardening and hobby chemicals, and kitchen items (eg, alcohol) should be kept out of reach of children. Visitors to the household should also be cautioned to keep medications out of reach of children. Substances should never be stored in unmarked containers, particularly in containers that typically hold beverages (eg, old soda bottles, cups). Medications should not be referred to as "candy" to entice youngsters to take them. Family members and visitors should be asked to store medications out of the child's reach and to dispose of leftover medications and used transdermal patches safely. Used transdermal patches may still contain up to 75% of the medication dose. Additionally, chewing on patches, as toddlers may do, releases the medication much faster. Parents and caregivers should have the universal telephone number for the poison control center and telephone numbers for local emergency departments readily available. Carbon monoxide detectors should be placed near children's bedrooms. Activated charcoal for home use is controversial and not currently recommended, although it is available without prescription from many pharmacies. Parents should not give activated charcoal without first speaking to poison control center staff or medical personnel.

Prognosis

Prognosis depends on the toxicity of the substance ingested. For a few substances, a small amount can be fatal (Box 82.4), whereas for others, even large ingestions are generally benign. Prognosis is generally excellent; fatalities in children are rare. Prognosis is worse for intentional ingestions, often because patients delay or do not reveal that they attempted overdose.

Box 82.4. Substances Potentially Fatal in 1 to 2 Pills or Teaspoons

- Camphor (found in Vicks VapoRub, Campho-Phenique, Tiger Balm)
- Imidazoline decongestants (found in over-the-counter nasal drops and eyedrops)
- Acetonitrile nail glue remover
- Clonidine hydrochloride (also available in transdermal patches)
- Opiates (also available in transdermal patches)
- Methyl salicylate (oil of wintergreen, Bengay)
- Calcium channel blockers
- Toxic alcohols (ie, methanol, ethylene glycol, ethanol, isopropanol)
- Tricyclic antidepressants
- Diphenoxylate and atropine (eg, Lomotil)
- Sulfonylurea oral hypoglycemics
- Chloroquine and hydroxychloroquine sulfate antimalarial agents
- Hydrofluoric acid
- Selenious acid (gun bluing solution)
- Buffered saline solution
- Benzocaine-induced methemoglobinemia

CASE RESOLUTION

Because the respiratory rate of this 2-year-old is slow and the child exhibits symptoms of miosis and altered level of consciousness narcotic ingestion is suspected, and naloxone is administered. The child becomes more alert, and respiratory rate increases to 24 breaths per minute. The father is instructed to retrieve the bottle, and the substance is found to be a prescription narcotic analgesic left in the house by a recent visitor. The child is given activated charcoal, observed overnight in the hospital, and discharged on the following day without sequelae.

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CHAPTER 83

Disaster Preparedness

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CASE STUDY

A family comes in for a well-child visit with their 7-year-old son and 9-month-old daughter, the latter of whom has complex congenital heart disease. The mother is concerned after a recent tornado in the next town resulted in prolonged power outages. She is wondering what the family might do in this situation. The daughter needs daily breathing treatments and often requires oxygen at nighttime. She is on multiple medications and a special formula. All her specialty doctors are at the children's hospital, which is more than an hour from their house. She is also concerned because her husband has a seizure disorder that requires medication. She asks whether the family should stay together in a disaster or separate to get her daughter to the children's hospital.

Questions

1. What are the 4 phases of disaster preparedness with which the pediatrician should be familiar?
2. What should be included in disaster preparedness kits? How should medications for all family members be included?
3. When should a family consider getting a backup generator?
4. What is the role of the local hospital and emergency medical services for the family with a child or children with special health care and critical medical needs?
5. What should the pediatrician recommend to the family about children's immunization records and important medical history?
6. How does the physician assess for the effect of traumatic events on children and their families?

Disaster preparedness has become an increasingly relevant topic for children and their families. Although natural disasters, war, and pandemic infections have always threatened human populations, increasing population density, global warming, international trade, and terrorist threats have heightened our awareness of disasters and the need for preparedness. State and federal systems are an essential component of disaster preparedness, but significant delays in the delivery of resources can occur. Because of a growing need to address the availability of resources and inherently delayed response times of the state and national systems, disaster preparedness is important for families and local communities. Recent major disasters, whether human-induced events, such as the 2013 bombing during the Boston Marathon, or natural events, such as Hurricane Harvey, which devastated Houston, Texas, in 2017, demonstrate the vulnerability of communities and the need for extensive local preparation. In the first hours to days after a disaster, community response is vital to well-being, and the community needs to be prepared to play a greater role than was historically anticipated. As frontline health care providers and advocates for children, pediatricians have a particular responsibility to maintain a baseline understanding of chemical, biological, and radioactive exposures as well as emerging pandemic infections to provide guidance to families in the event of such disasters.

In addition to large-scale disasters, incidents in which local emergency medical services (EMS) are overwhelmed by the number and severity of casualties, termed *mass casualty incidents*, also have the potential to overwhelm community resources. These may include catastrophic events, such as multiple-vehicle collisions, mass shootings, and hazardous materials spills. Patients must be quickly triaged, treated, and transported. Typically, local government facilitates the initial response in accordance with emergency preparedness policies and procedures. This may include coordinating efforts with surrounding communities as per regional preparedness plans, along with additional assistance as necessary from state government. A public health emergency is declared only when an event exceeds the ability of local, regional, and state resources to provide routine care as the result of any incident that poses substantial risk for human fatalities or long-term disabilities. Preparedness experts suggest evaluating public health emergencies from what is called an *all-hazards approach*, which focuses on the key elements necessary to ensure the provision of routine care during any type of disaster or mass casualty incident. Specific scenarios that occur rarely, such as chemical or radiation exposure, require access to specialized resources that may be impractical to stockpile or are limited in availability. From a practical standpoint, the all-hazards approach is more effective.

Multiple factors make children more vulnerable than adults during a disaster. In the United States, children make up approximately 25% of the population. Younger children, especially, are reliant on others for food, shelter, and, importantly, psychological support. Their unique nutritional needs put them at risk for malnourishment if specific dietary requirements are not available. Additionally, children often have less mature immune systems. In a setting of physical stress and unreliable sanitation, children are at increased

risk for infection. Moreover, decreased fluid reserves make children more susceptible to blood loss or dehydration from agents that cause diarrhea and vomiting. In the setting of a blast or fall, children are at increased risk for traumatic brain injury because of their large head-to-body ratio. Their more pliable skeleton also increases the likelihood for internal organ injury. Furthermore, children are at increased risk for exposure from chemical, biological, and radiation disasters because of their unique physiology. Infants and children have higher minute ventilation, resulting in increased inhalation of aerosolized agents. Their smaller height increases their exposure to high-vapor density agents, which are in higher concentrations closer to the ground. Additionally, the skin of infants and children is more permeable because of lesser keratinization compared with adults, and infants and children have a larger surface area-to-body mass ratio. As a result, exposed children receive a higher dose of transdermally absorbed toxins than adults exposed under identical circumstances. This larger surface area-to-body mass ratio also complicates treatment, because children are at increased risk for hypothermia during the decontamination process. Finally, the psychological effect of being separated from family and experiencing other disaster-related trauma can be devastating in the short- and long-term.

The 4 phases that the pediatrician should understand when it comes to disaster preparedness and the importance of advocating for children at each of these steps are planning, rescue, recovery, and mitigation. *Planning* includes training and education as well as identifying specific local risks. For example, some communities might need to anticipate hurricanes and flooding, whereas others are more concerned about earthquakes or blizzards. This is a key area in which the pediatrician can intervene and both work with families to develop disaster plans and interact with the local disaster response community to improve the capacity to care for children. *Rescue* refers to the actions taken during a disaster, and this is typically what receives the most attention in the media and by the public. *Recovery* is the process that begins immediately after the disaster occurs—often simultaneously with the rescue phase—in which the community works toward returning to normal routines. This is also the phase during which mental health problems begin to emerge. *Mitigation* is an important and often overlooked phase in which individuals and the community learn from the response to the disaster to prevent future occurrences or improve on the response to decrease the effect of future disasters.

Unfortunately, many disaster response teams lack pediatric training, protocols, and equipment. Recently, various public health and disaster organizations have lobbied for states to mandate disaster preparedness regulations for children. Specifically, many states lack basic emergency preparedness regulations for schools and child care facilities. The developmental vulnerabilities of infants, toddlers, and young children make them physically less able to escape a disaster scene and cognitively less able to recognize the need to flee and follow directions from authorities. Children with special health care needs, whether because of physical or cognitive disabilities, require specific attention. The pediatrician can assist schools and child care centers in developing disaster preparedness plans. All child care facilities should have a plan in place that addresses all-hazards safety, medical needs, evacuation and transportation, and reunification with families. The idea of family-centered care that seeks to keep family units together even as care is needed for individual members is important for the immediate physical health and long-term mental health of children during and after disasters.

The Role of the Pediatrician With Families

The pediatrician serves as an important resource for disaster preparedness planning for families. The pediatrician should consider assessing a family's level of readiness for a disaster and then tailor anticipatory guidance accordingly. Families must stay informed and realize that everyone is susceptible to some type of disaster. The pediatrician can also ensure that families understand the importance of preparation and the special needs of children during a disaster. The US Federal Emergency Management Agency (FEMA) offers a free smartphone application (www.fema.gov/smartphone-app) that includes specific information on various types of natural disasters, how to build a disaster kit, resources for victims of disasters, and a disaster reporting feature. Families should prepare an emergency kit that provides up to 3 days of basic necessities, including food, water, and clothing. Families of newborns and infants must include formula and diapers as well as any daily medications for all family members. Copies of immunization and general medical information are useful as well as pictures of family members in case the family unit is separated. Parents must be prepared to handle nonemergent problems, because formal medical care may be limited to the seriously ill and injured during a disaster. If a family needs acute medical care, it may be necessary to treat children in adult facilities; alternatively, for the family unit to remain together it may be necessary for adults within the family to undergo treatment in pediatric facilities. The more information families can provide about any medical conditions requiring attention, the easier it will be to receive appropriate care in a disaster.

Families of children with special needs are especially vulnerable after a disaster because access to routine medical care may not be available. Experience in Japan during the 2011 earthquake and subsequent tsunami showed increased mortality among children with special needs and increased hospitalizations for children who were technology dependent. Not only should families have a sufficient supply of medication, they should have a surplus of necessary medical equipment and nutritional supplements. Common supplies, such as a feeding tube or catheters, may be in short supply or unavailable during a disaster. Families with a child on a ventilator or one who is oxygen dependent should notify local utilities to flag their address for priority status during power outages. They should consider the benefits of backup battery units and a backup generator at their home. These families would also benefit from notifying their local EMS agency and hospital of their child's medical needs, because some EMS systems keep a registry of children with special

needs. Some communities have developed systems in which posters are disseminated for placement in a window of the home specifying if any occupant may require special services from EMS in the event of a disaster or terrorist attack. Additionally, the American Academy of Pediatrics (AAP) and American College of Emergency Physicians offer an emergency information form that can be completed with the pediatrician and should be part of the emergency preparedness kit. The emergency information form contains information on diagnoses, procedures, medications, common presenting problems, and suggested medical management (see Online Resources). The family of a child with special needs can also contact the National Organization on Disability (www.nod.org) or Family Voices (www.familyvoices.org) for more detailed information on preparing for a disaster.

During the recovery phase after a disaster, children and adolescents may develop chronic medical problems as a result of injuries sustained during the event. Beyond physical injuries, all disasters have a psychological effect on children. The experiences and effects of disaster are unique to each patient, and the pediatrician must individualize treatment accordingly. Multiple studies of various types of disasters demonstrate the increase in mental health symptoms among children and adolescents exposed to a disaster. This is true even if a family is not directly affected by the disaster but is exposed to the event within the community, on television, or through the internet and social media. A child may present with somatic symptoms, such as headaches and abdominal pain, or may not want to participate in his or her normal activities. Long-term effects include depression, anxiety, aggression, and substance abuse. Age-appropriate discussions should be encouraged along with validation of the child's concerns while assuring the safety of the individual child. Posttraumatic stress disorder should be considered in the differential diagnosis of the patient with persistent symptoms that do not respond to family support. Families and health professionals can obtain further information through the AAP (www.aap.org) and the Substance Abuse and Mental Health Services Administration (www.samhsa.gov).

The Role of the Pediatrician in the Community

Many state and regional disaster preparedness plans are tailored for an adult population and may not consider the special needs of children. The pediatrician can participate in the development of a community-wide disaster preparedness plan (eg, identifying emergency meeting locations) as well as surveillance to identify potential disasters as part of the planning phase of disaster response. From an operational standpoint, it is more effective to have 1 plan that can take into consideration the needs of multiple vulnerable populations rather than a separate disaster preparedness plan for each population. The pediatrician should serve as a consultant about local preparation and provide guidance about the unique medical, nutritional, and psychological needs of children. For example, increased staffing needs should be anticipated when caring for younger children and infants. Depending on availability of human milk, newborns and infants may require formula and a sterile water supply. The food needs of young children differ from those of adults. Stockpiling of medications for biological, chemical, or radiation disasters must take into consideration dosing differences for children compared with adults. It is necessary to make available suspensions of medications in addition to pill forms. Furthermore, many recommended antidotes and treatments are not approved for use in the pediatric population, and policies on the risks and benefits of their use in disasters should be established.

Emergency medical services systems are charged with the initial and rapid triage of all victims. Various well-known triage algorithms are available, including sort, assess, lifesaving interventions, treatment/transport (SALT) and simple triage and rapid treatment (START). Common to all is the rapid sorting of patients based on ability to ambulate followed by assessment of respiratory status, circulation/perfusion, and motor skills. Although multiple triage tools exist, the physiologic parameters and mental status assessments used in adult-based algorithms may not be suitable for children of all ages. Triage systems must take into account physiological differences of children as well as their psychological response to strangers. For example, young children may not be able to communicate their complaint, and because their vital signs are normally different from those of adults, medical personnel accustomed to working with adults may misinterpret physical findings and overtriage children. JumpSTART is a widely recognized pediatric-specific disaster triage tool that parallels START but is customized to address a child's developmental ability and age-appropriate vital signs. However, it fails to capture children who are dependent on technology or those with special health care needs. Whether or not a triage tool is readily available, clinical decision making can be relied on to help sort and triage victims in a disaster.

Ideally, children should remain with their caregiver as part of family-centered disaster care. If this is not possible, it is necessary for a child advocate to be with the child at all times, although the nature of disaster response may make this challenging if not planned in advance. Additionally, incorporation of child life specialists and techniques for distraction during medical procedures should be encouraged. Children may not respond well to new environments and disaster protocols. The simple process of decontamination can be devastating to a young child without the presence of a parent or other familiar caregiver. A child may have concerns about being sprayed with water or may refuse to disrobe in front of strangers, which may affect the success of decontamination for children and adolescents. It is assumed that adults will comply with protocols, but such compliance is less predictable in a pediatric population. A child may be afraid of strangers or may simply wander off before triage is complete. Nonmedical personnel or bystanders may be called on to assist with supervising ambulatory children.

Facility-based issues must also be addressed in regional disaster preparedness plans. These include providing for increased staffing in adult facilities caring for children as well as the need for stockpiling of pediatric supplies at those facilities. Similarly, parents may be triaged with their children, so pediatric facilities should be prepared

to manage adult victims as well. Additionally, facilities need to plan for children arriving without a caregiver and establish an identification system that allows children to be reunited with their families. This was a significant problem for children displaced during Hurricane Katrina. Strategies to address this include using digital cameras to photograph children on arrival with their original clothing as a means of facilitating family reunification.

The Role of the Pediatrician in Disaster Surveillance and Management

Pediatricians function as key public health workers. Their knowledge and diligence aids in local and regional surveillance for potential chemical, biological, and radiation disasters. Families may seek care from their pediatrician rather than an emergency department for early symptoms during and after a disaster. Although it is beyond the scope of this chapter to provide details about signs and symptoms after every type of disaster, important concepts in identifying and treating patients with exposures to chemical and biological agents as well as radiation are highlighted herein.

Chemical exposures usually result in immediate symptoms and require special protection for emergency personnel as well as decontamination for the victims. These exposures can occur from terrorism as well as (more commonly) industrial accidents. Insecticides, herbicides, and nerve gases are organophosphates that inhibit the enzyme acetylcholinesterase. This results in the accumulation of acetylcholine and excessive cholinergic stimulation at muscarinic and nicotinic receptors. Symptoms include the muscarinic SLUDGE toxidrome (increased salivation, lacrimation, urination, diaphoresis, gastric distress, and emesis) as well as the MTWHF nicotinic toxidrome (mydriasis, tachycardia, weakness, hypertension, and fasciculation). Vesicant exposure, such as mustard gas and lewisite, causes irreversible damage to mucous membranes, skin, and the respiratory system soon after exposure. Cyanide is another common chemical agent, known for its bitter almond taste. Cyanide inhibits cellular metabolism and causes rapid hypotension, coma, seizures, and death. Agents other than nerve agents usually do not result in severe mortality but rather incapacitate the victim. Many other chemical agents from industrial accidents can cause a variety of skin and pulmonary symptoms.

Biological agents include bacteria, viruses, and preformed toxins. These agents may be easy to disperse and can affect large populations. Unlike in chemical exposures, the onset of symptoms is delayed by hours to days, and symptoms are more difficult to distinguish from common ailments. Secondary transmission of the infection is also of concern with some agents. Management of biological disaster requires detailed surveillance and containment of exposed populations.

Although there are too many biological agents to discuss in any detail in this brief chapter, a few of particular relevance to disaster planning are mentioned here. Anthrax, from *Bacillus anthracis,* is a gram-positive sporulating rod. When used as a bioterrorism agent in its inhaled form, victims present with severe influenza-like symptoms with an associated high fatality rate. Fever and dyspnea associated with a widened mediastinum are common and may progress to shock. Ciprofloxacin and doxycycline are recommended for prophylaxis and treatment among adults. Despite the risks to bone and cartilage that generally restrict its use to healthy children, ciprofloxacin is approved by the US Food and Drug Administration (FDA) for use in children with inhalational anthrax exposure. Doxycycline should generally be avoided in children younger than 8 years, although it may be considered on a case-by-case basis. The physician must consider consulting with experts to assist in assessing the risks and benefits associated with using these medications. Among the viruses, variola, more commonly known as smallpox, is an agent of concern. After its global eradication in 1980, children were no longer immunized, leaving all children and most adults susceptible to the virus. Similar to varicella (ie, chickenpox), it presents with vesicles with umbilicated centers but is associated with a higher mortality rate of 3% to 30% among nonimmunized individuals. Exposure to the potent botulinal toxin results in cranial nerve disturbances, descending paralysis, and respiratory distress. Ricin, which is derived from the castor bean, is another potent toxin. Inhalation results in fever, cough, and pulmonary edema, often resulting in death within days. Ingestion presents with severe vomiting and diarrhea, resulting in hypovolemic shock. For a complete list of biological agents, presenting symptoms, and potential treatment or prophylaxis, physicians should consult the Centers for Disease Control and Prevention.

Radiation exposure may occur as a result of damage to a facility containing nuclear material, detonation of a nuclear weapon, or dispersal of nuclear material by a radioactive dispersal device. Ionizing radiation presents the greatest health risk because of its high-frequency energy. It causes chromosomal breaks in cells that can cause long-term damage and increased risk of cancer. The 5 types of ionizing radiation with specific characteristics, behaviors, and toxicities are alpha particles, beta particles, gamma rays, x-rays, and neutrons. Alpha particles have limited ability to penetrate but when inhaled or ingested can cause internal damage. Beta particles are most commonly found in a medical setting, and they have greater penetration than alpha particles. Beta particles can cause skin damage as well as damage when ingested. Gamma rays and x-rays are part of the electromagnetic spectrum. Gamma rays are high energy and cause significant damage. This type radiation would be seen after a nuclear detonation or from radioactive materials. Much less common are neutrons, which induce radioactivity. Exposure to radiation is classified as external, internal, whole body, and partial body. The effects of radiation can directly damage the target tissue, or the effects can be indirect, caused by the creation of free radicals. Tissue sensitivity is based on the cellular rate of division and level of differentiation. The most sensitive to least is as follows: lymphoid, gastrointestinal, reproductive, dermal, bone marrow, nervous system. The severity of exposure is also dependent on the dose of radiation, type of radiation, and age of the victim.

Radiation exposure is quantified by the amount of energy absorbed (ie, rad [radiation absorbed dose]) and the relative

biological effectiveness of doses (RBE) based on the type of ionizing radiation. The rem is the product of the rad and RBE. Under the International System of Units, the rad and rem are being replaced by the gray (1 Gy = 100 rad) and sievert (1 Sv = 100 rem). Typically, doses for common radiation exposures are given in millisieverts (1 mSv = 0.001 Sv). Radiation exposure from common radiographic procedures can range from 0.1 mSv for a chest radiograph to 2 to 20 mSv for a computed tomography scan.

Symptoms associated with radiation exposure depend on the total exposure. Nausea and vomiting can present with exposures of 0.75 to 1 Gy and lymphoid and bone marrow suppression with exposures of 1 to 6 Gy. The mean lethal dose, the radiation dose for which one-half of the population is expected to die within 60 days, is 4 Gy. Long-term effects of radiation include increased incidence of cancer and psychological distress. Evacuation is the ideal intervention to decrease exposure, but this may not be feasible in a timely fashion in highly populated areas.

Seeking shelter can greatly decrease the level of exposure, with large cement structures providing the best protection. The use of potassium iodide is effective in exposures to radioactive iodine, which is associated with nuclear power facilities. It can be dispensed in a pill and in suspension form. Dosage is based on level of radiation exposure and patient age, and physicians should consult the FDA (www.fda.gov) or the US Nuclear Regulatory Commission (www.nrc.gov) to determine the appropriate dosage of potassium iodide depending on the level of radiation exposure. For individuals seeking medical care, containment and decontamination are essential. Removal of clothing and washing the skin with warm water is quite effective. Supportive medical care is essential in managing patients with radiation exposure. Radiation results in significant immune suppression, neutropenia, and lymphocytopenia, which last for weeks and need close monitoring. The physician should be aggressive in managing infections and consider treatments to increase bone marrow regeneration. Expert consultation in radiation sickness would be prudent.

In addition to caring for patients, pediatricians need to take into consideration the well-being of their own family as well as that of office staff. During a disaster, office staff may not be able to get to work. For those able to report to work, extra supplies of food and water must be available in case staff cannot return to their homes. An office disaster plan should be implemented with emergency contacts and preparation for the staff's basic needs. Basic medical supplies should be available to care for patients during a disaster. Depending on the type and severity of the disaster, access to the office facility may be prohibited. Plans for backing up patient medical records should be implemented as well as for alternative sites in which medical services can be delivered.

Physicians need to review their medical liability policies addressing the provision of care in a disaster situation. Most policies only provide coverage for care that is provided in the office setting. Good Samaritan laws vary in each state about what level of protection is provided to the health professional. The AAP recommends that during a disaster situation, pediatricians who volunteer do so under the auspices of an official disaster agency or recognized relief organization to ensure the greatest protection from liability.

Conclusion

The pediatrician has a vital role in predisaster, disaster, and postdisaster management on the local, regional, state, and national level, not only as a medical service professional but also as an advocate for the special needs of children and their families. The essential components of disaster management are to provide for all basic human requirements, reduce an individual's vulnerability to disasters, and, after a disaster has occurred, reduce the exposure risk. The pediatrician can educate and assist families in preparing for disasters. Additionally, the pediatrician can guide communities in their disaster preparedness planning to accommodate the particular vulnerabilities of children. As with other health professionals, pediatricians can also contribute to the essential medical and public health workforce during a disaster. Pediatricians can access the most current guidelines and recommendations through multiple professional and governmental resources. It is imperative for the physician to have easy access to telephone numbers and websites specific to pediatric disaster preparedness and response for the relevant local, state, and federal agencies.

CASE RESOLUTION

The family is relieved to discuss the importance of preparing for a disaster. They now have an idea of what is involved in disaster preparation and feel less vulnerable. They plan to create and store an emergency kit with a 3-day supply of food, water, and medications as well as a first aid kit. Additionally, they will refer to the FEMA application for further recommendations. Together with their pediatrician, they complete an emergency information form for the kit. In the event of a disaster, they plan to stay together. The mother also shares her plan to call their local utility company to identify their house as a priority during a power failure and indicates she will consider purchasing a backup generator. Before leaving the office, the mother shares that her son has been sleeping less since the tornado and does not want to go to school because he is afraid of being away from the family. The pediatrician encourages the family to discuss the boy's fears while ensuring his safety. Having the son participate in making the emergency kit and creating a family plan may help. A follow-up visit is scheduled to reassess his symptoms and decide if further intervention is needed.

Online Resources

American Academy of Pediatrics
www.aap.org/disasters
Children and disasters: disaster preparedness to meet children's needs.

American College of Emergency Physicians
www.acep.org/disaster
EMS and disaster preparedness.

Centers for Disease Control and Prevention
https://emergency.cdc.gov/children
Caring for children in a disaster.

Family Voices
http://familyvoices.org/wp-content/uploads/2010/10/Disasters_Emergencies-tip-sheet-final-5.23.18.pdf
Disasters and emergencies: keeping children and youth safe.

National Safety Council
www.nsc.org/safety_home/emergencypreparedness/Pages/EmergencyPreparedness.aspx
Emergency preparedness: are you ready for a disaster?

US Department of Health and Human Services Assistant Secretary for Preparedness and Response
www.phe.gov/Preparedness/planning/abc/Pages/webinar-resources-130620.aspx
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PART 6

Head, Neck, and Respiratory System

CHAPTER 84

Approach to the Child With Dysmorphism

Henry J. Lin, MD, and Moin Vera, MD, PhD

CASE STUDY

A 13-year-old boy presents to the office for the first time for an evaluation after moving to the area. His parents note that he has unexplained intellectual disability and has had problems with hyperactivity in school. The pregnancy was uncomplicated and the mother, who was a 32-year-old gravida 1, para 1 at the time of the child's birth, denies alcohol or drug use or exposure to any teratogens during pregnancy. Delivery was by cesarean section secondary to cephalopelvic disproportion, but the Apgar score was 8 at 1 minute and 9 at 5 minutes. As a newborn the patient was noted to have macrocephaly and to be large for gestational age. He did well in the newborn period and had no feeding problems. Subsequently, he had no significant medical illnesses, including no seizures, but at 1 year of age he was noted to be developmentally delayed. This delay continued, and he has been in special education classes throughout his schooling. Family history is negative for any relatives with disabilities.

On physical examination, the boy is at greater than the 90th percentile for height and weight. He exhibits mild prognathism with large ears. His fingers are hyperextensible. A complete physical examination reveals that his testicles appear large (6 cm), and his sexual maturity rating (ie, Tanner stage) is 3. The rest of the examination is normal.

Questions

1. What history is important to elicit in evaluating a child with dysmorphic features?
2. What are the possible causes of errors in morphogenesis?
3. What clues on physical examination can aid in establishing a specific diagnosis?
4. What laboratory tests can confirm a diagnosis?
5. When is it appropriate to obtain a genetics consultation or refer a patient for genetic counseling?
6. What are the benefits of establishing a specific diagnosis?

Evaluation for structural anomalies is an essential part of all pediatric examinations. Visible errors in morphogenesis are a source of potentially useful information in the evaluation of a patient with abnormal symptoms, such as seizures. Additionally, major malformations frequently require treatment, and the presence of 1 anomaly suggests that others may also exist.

The study of congenital defects was termed *dysmorphology* by David Smith, MD, in 1966. The anomalies fall into 2 categories: minor and major. Minor malformations are those of "no medical or cosmetic consequence to the patient." An example is a supernumerary nipple that appears as a hyperpigmented papule along the nipple line. Identification of minor malformations is important, because they may indicate the presence of a more generalized pattern of malformation. Major malformations are those that have "an adverse effect on either the function or social acceptability of the individual." Cleft lip and palate are major malformations that have functional as well as cosmetic relevance to the patient's health. Severe congenital malformations as defined by the Centers for Disease Control and Prevention are "defects that cause death, hospitalization or intellectual disability; necessitate significant surgical procedures; are disfiguring; or interfere with physical performance."

Epidemiology

Structural anomalies are common in the general population. Most are minor. In the first comprehensive analysis of minor structural anomalies, Marden in 1964 reported that 7% to 14% of newborns have at least 1 minor anomaly on surface examination. Other studies indicate that up to 40% of newborns have 1 anomaly. The presence of 3 or more minor malformations has predictive value in identifying a major malformation. Among newborns, 0.8% have 2 minor malformations, and 11% of these patients have a major malformation. Three or more minor malformations occur in 0.5% of newborns, and 90% of these patients have a major malformation. Data from the National Collaborative Perinatal Project revealed that 44.8% of these anomalies were craniofacial manifestations and 45.3% were skin abnormalities. Autopsies of expired fetuses show an increased incidence of minor and major malformations. Males are affected with minor malformations more often than females. Frequencies of minor

and major malformations vary along racial lines, depending on the specific malformations. For example, postaxial polydactyly occurs in 16 of 10,000 births among whites and in 140 of 10,000 births among blacks. Hemangiomas occur in 350 of 10,000 births among whites, whereas the frequency among blacks is 100 in 10,000 births.

Three percent of all pregnancies produce a child with a significant genetic disease or birth defect. These malformations account for a great proportion of morbidity and mortality in the pediatric population. Of all pediatric hospital admissions, 33% to 50% involve a child with a disease with a genetic component.

Clinical Presentation

With the advent of various prenatal tests and diagnostic modalities, detection of anomalies may occur during pregnancy. Abnormalities on routine prenatal screening raise the possibility of finding an anomaly in the newborn. For example, an elevated maternal α-fetoprotein may be indicative of a neural tube defect. Amniocentesis or chorionic villus biopsy may reveal abnormal chromosomes associated with malformations. Standard prenatal ultrasonography examinations can demonstrate structural defects in utero, which can be further delineated on specific fetal ultrasonography examinations. More recently, maternal plasma cell-free DNA has been used for noninvasive prenatal testing for trisomy syndromes.

Most structural anomalies develop during the first trimester of gestation and, if not detected prenatally, are noted in the delivery room or newborn nursery (see Chapter 25). Many major congenital defects are obvious on a thorough physical examination. Other major defects, such as a tracheoesophageal fistula, are not evident on clinical examination but become readily apparent as the neonate adapts to extrauterine life and experiences difficulties with feeding. Minor anomalies may be overlooked on initial newborn examination. If developmental disability manifests by age 6 months in an infant who exhibited minor anomalies as a newborn, however, the physician should thoroughly evaluate the infant for minor anomalies that may aid in identifying the cause of the condition.

Sometimes dysmorphic features are not present at birth but become apparent as the child grows and develops. Such features may be associated with dysplasias, that is, defects in cellular metabolism that manifest after birth (eg, skeletal dysplasia that becomes more apparent as the bones grow).

Pathophysiology

In terms of pathophysiology, structural defects can be separated into 4 different types of errors in morphogenesis: malformation, deformation, disruption, and dysplasia (Box 84.1). All these types of errors can result in a sequence of abnormalities.

Previously, the term "malformation" was used descriptively to denote an anomaly; however, it is also used to denote a specific pathogenic mechanism. A *malformation* is a permanent defect in a structure caused by an intrinsic abnormality in the development of that structure. An example of a malformation is an endocardial cushion defect in a patient with Down syndrome. Malformation syndromes frequently are caused by chromosomal abnormalities, single-gene disorders involving genes that program for structure, or environmental teratogens. Teratogens interfere with organ development during a critical period in embryogenesis, resulting in organ dysgenesis. Alcohol, certain drugs, x-ray irradiation, viral infections, and other environmental exposures can all be teratogens. More than 30 drugs have been proven to be teratogenic.

Box 84.1. Pathophysiology of Structural Defects

Malformation
- Chromosomal abnormality
- Single gene disorder

Deformation

Disruption
- Vascular compromise
- Viral infection
- Mechanical (eg, amniotic bands)
- Teratogens (eg, alcohol, drugs, irradiation)

Dysplasia
- Metabolic or structural protein disorder

Deformation results from exertion of mechanical pressure by external forces on the developing fetus. This mechanism involves no intrinsic defect of the fetus. Deformation associated with intrauterine forces can be caused by uterine constraint, an abnormally shaped uterus, or multiparous pregnancy. For example, flexible talipes equinovarus (ie, clubfoot) is a deformation caused by uterine constraint. Postnatal deformations can also occur, such as plagiocephaly caused by an infant sleeping on his or her back.

With *disruption*, an agent outside the fetus causes cell death, resulting in a permanent defect in fetal development. Disruptive events result in tissue destruction. Examples of disruptive events are tissue ischemia secondary to vascular compromise, viral infection at a critical gestational age (eg, Zika virus infection), and mechanical interference with normal development. An amniotic band is an example of a mechanical disruptive agent; an amniotic band can cause amputation of a developing limb by restricting blood flow to it.

Dysplasias, which often are caused by a single-gene defect, are structural abnormalities that occur as the result of abnormal cellular metabolism and/or organization. Dysplasia can be apparent in utero (and therefore at birth [eg, skeletal dysplasia]) or later. Mucopolysaccharidosis type I causes dysplasias that manifest postnatally secondary to absence of the lysosomal hydrolase, α-L-iduronidase. Glycosaminoglycans accumulate in parenchymal and mesenchymal tissues after birth. Affected children develop coarse facies, an enlarged tongue, misshapen bones, and hepatosplenomegaly, among other features.

Differential Diagnosis

In generating an appropriate differential diagnosis for a child with dysmorphism, it is essential to identify all minor and major malformations. The differential diagnosis varies depending on the specific findings. A thorough patient history and physical examination are necessary to aid in establishing the list of conditions to consider. For the patient with multiple anomalies, identifying the most specific and rarest anomaly can direct the health professional to a narrower list of possible diagnoses. For example, nail hypoplasia, which occurs in fetal hydantoin syndrome, is much rarer than congenital cardiac disease, which occurs in multiple syndromes. The health professional should be familiar with the prominent features of the more common syndromes. Reference texts, such as *Smith's Recognizable Patterns of Human Malformation,* are helpful in establishing differential diagnosis lists and in finalizing diagnoses. In addition, several helpful websites are available, such as OMIM (Online Mendelian Inheritance in Man), PubMed, Google and Google Scholar, and others that were specifically developed for the delineation of syndromes and genetic disorders.

In evaluating a neonate or an infant with congenital anomalies, the physician should attempt to separate the findings into 1 of 5 categories: an isolated defect, a developmental field defect, a birth defect association, a sequence pattern, or a dysmorphic syndrome. The first step is to determine whether the anomaly is isolated. If so, does it represent a failure in development in 1 location, such as a cleft lip? Most *isolated anomalies* are believed to have a multifactorial inheritance, representing the interaction between multiple genes and unknown external influences. Typically, the risk of recurrence for isolated anomalies in future pregnancies is 2% to 5%.

A *developmental field defect* is a pattern of anomalies that occurs in structures that are in close physical proximity during embryologic development. The defects may involve a limited region and may be the result of a single disruptive event (eg, vascular compromise); thus, the risk for recurrence in subsequent pregnancies is low. One example of such a defect is hemifacial microsomia (ie, oculoauriculovertebral defect), which is believed to be caused by disruption of vascular flow to the first and second branchial arches. The disruption results in hypoplasia of the malar, maxillary, and mandibular region on 1 side with associated microtia and vertebral defects.

Birth defect associations are those in which a combination of anomalies occurs together frequently but the pattern does not fit a known field defect or syndrome. Etiologies of association defects may be unknown, and risk for recurrence in subsequent pregnancies may be low. One of the more common associations is the VACTERL association (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal defects, and limb defects).

A *sequence pattern* of anomalies occurs when 1 malformation results in multiple dysmorphic features. For example, oligohydramnios sequence with Potter facies results from renal agenesis. The renal malformation causes oligohydramnios, which in turn causes fetal joint contractures, pulmonary hypoplasia, and a flattened face.

A *syndrome* is a constellation of anomalies that are pathogenetically related. Chromosomal abnormalities (eg, trisomy 21), single-gene disorders, and teratogens can produce syndromes. Alcohol is the most common teratogen to which fetuses may be exposed. Alcohol exposure in utero causes growth failure, intellectual disability, microcephaly, a short nose, and small distal phalanges (see Chapter 147). Children with intellectual disability and structural anomalies are at increased risk for having a syndrome and should undergo genetic or genomic testing.

Evaluation

History

A complete history is essential (Box 84.2). The history begins prenatally with information from the mother on duration of pregnancy, possible teratogen exposure, fetal activity, diagnostic test results, and any complications of pregnancy. The delivery history should include information on the type of delivery, newborn presentation, and size at birth, including growth percentiles. Neonatal adaptation and feeding patterns are important parameters to assess. The subsequent medical history also should be obtained. The identification of associated intellectual disability is an essential part of the history.

A thorough family history is equally important, including a pedigree. Specifically, the family should be questioned about parental ages, information pertaining to possible consanguinity, and any history of fetal loss or early infant deaths. Family histories of birth defects or disabilities should be documented.

Physical Examination

The physical examination should be extremely thorough, and all morphologic findings should be noted. As previously mentioned, the craniofacial area and skin are common sites for anomalies, but all organ systems should be extensively evaluated. Even minor anomalies, such as a supernumerary nipple or clinodactyly, may have

Box 84.2. What to Ask

Child With Dysmorphism

- How long was the pregnancy?
- Did the mother take any medications, smoke cigarettes, or use alcohol or any illicit drug?
- What was the fetal activity?
- Were there any complications of pregnancy?
- What was the type of delivery and presentation of the baby?
- What was the newborn's size at birth?
- How did the newborn feed?
- What is the subsequent medical and developmental history?
- Are the parents related?
- What are the ages of the parents?
- Is there a history of fetal or infant deaths?
- Is there a history of birth defects in the family?
- Do any family members have disabilities?

significance. Objective measurements should be obtained when possible. Normal growth curves are available for evaluating measurements of the face (and other body parts), such as inner canthal distances, palpebral fissure lengths, and ear lengths. Unusual hair whorl patterns and dermatoglyphics (eg, appearance of the palmar creases) should be noted. Physical data, including height, weight, and head circumference, should be plotted and the growth percentiles checked. A complete ophthalmologic evaluation may be indicated to detect abnormalities such as cataracts or cherry-red spots.

Laboratory Tests

In assessing children who appear dysmorphic, the physical examination is the most important part of the evaluation. Findings on physical examination help guide selection of laboratory tests. Additional studies may then confirm a suspected diagnosis. Similarly, when prenatal screening detects an abnormality, specific prenatal tests may be used to assess the fetus for associated disorders.

Cytogenetic testing has been a major tool for evaluating children suspected of having a chromosome disorder, and it also has been used for children with malformations and intellectual disability. Chromosomal microarrays have largely replaced standard chromosomal analysis, because microarrays are better for detecting copy number variants, such as chromosome deletions or duplications. The older methods (eg, G-banded karyotyping, fluorescence in situ hybridization) are still used in certain situations, however, such as in distinguishing between trisomy 21 versus Down syndrome involving a translocation.

Whole-exome sequencing and gene sequencing panels have become important components of dysmorphology evaluations and are often performed as first-line testing. Whole-exome sequencing is a powerful tool for uncovering single-gene disorders and has also been used to detect Turner syndrome, which is a chromosomal disorder (45,X). Whole-genome sequencing is starting to be used clinically and offers greater detection ability compared with whole-exome sequencing, because sequences obtained are not limited to coding regions. Consultation with a medical geneticist is helpful in selecting the most appropriate tests for specific situations. Also, the possibility of detecting findings of unknown clinical significance needs to be addressed, before whole-exome or -genome sequencing is used.

Some syndromes can be detected by metabolic testing. For example, Smith-Lemli-Opitz syndrome is a malformation syndrome caused by a disorder in cholesterol metabolism. Plasma amino acids, urine organic acids, and a plasma acylcarnitine profile are examples of metabolic tests that are widely available. Many of the analytes on these tests are also included in state newborn screening protocols.

Imaging Studies

Imaging studies are extremely useful in deriving information on internal malformations. Radiographs, including skeletal surveys, may detect skeletal anomalies. Echocardiography, renal ultrasonography, computed tomography, and magnetic resonance imaging studies all can be used when appropriate. With the findings of anomalies and global developmental delay in a patient, the American Academy of Neurology recommends routine neuroimaging with magnetic resonance imaging.

Management

Children who present with dysmorphic features should be evaluated to determine a specific diagnosis, if possible. Obtaining a diagnosis is of vital importance for patient care and parental counseling. Knowing the diagnosis can direct testing for associated abnormalities. Treatment options may be available, and a prognosis can be established. Defining the developmental prognosis for children is essential for school planning. If intellectual disability is not associated with the diagnosis, such as with cleft lip and palate, the primary care physician should reassure the parent or parents of that. Parents also need to know the risk for recurrence for future children. Occasionally, further testing of parents may be needed to accurately determine recurrence risks. For example, the risk for a chromosomal abnormality in a subsequent child is increased if 1 of the parents is a carrier of a balanced chromosome translocation.

Health supervision strategies have been established for specific disorders. For instance, published guidelines recommend hearing, ophthalmologic, and thyroid screening, among other tests, for patients with Down syndrome. The field of genetic diseases advances rapidly, and it is often difficult for the primary care physician to stay informed. A geneticist can provide guidance on up-to-date recommendations.

Parents may wish to be referred to support groups for specific conditions. Such groups can be invaluable in helping parents understand their child's condition and adjust to the disorder. They can also advise parents about community and educational resources and help parents advocate for their child's unique needs.

Referral to a genetic counselor can provide parents with information about prenatal testing, recurrence risk, and alternatives for addressing recurrence risks. Counseling is extremely useful in helping parents understand the mode of inheritance.

Prognosis

As with management, defining an accurate prognosis for each patient depends on recognition of the specific condition. Some conditions, such as trisomy 13, are lethal, whereas other conditions allow for a normal life span.

Malformations are permanent defects that generally have a recurrence risk. They may be correctable with surgery or treatment, but frequently there will be residual disability.

Deformations usually resolve with treatment and have no recurrence risk, except in cases in which the deformation is secondary to a uterine abnormality (eg, bicornuate uterus).

A disruption may be treated with surgery or therapy to improve function; however, as with malformations, residual disability frequently remains. For disruption resulting from tissue ischemia or a mechanical agent, no recurrence risk is expected. For disruption resulting from a teratogen, however, the disruption may recur with exposure to the same teratogen.

Dysplasias tend to persist or worsen with time, unless a specific treatment is available. Generally, a risk for recurrence exists. Specific treatments are available for only a limited number of diseases, although progress is being made, such as in the area of enzyme replacement therapy.

CASE RESOLUTION

The child has features that are suggestive of a dysmorphic syndrome. The most specific finding on examination is macro-orchidism. This finding is associated with fragile X syndrome. The patient is referred to a genetic specialist for diagnosis and counseling. Specific DNA-based molecular analysis is performed and is positive for a fragile site on the X chromosome at Xq27.3.

The parents are counseled that this condition has an X-linked inheritance mode. The child will have a normal life span but may need early intervention services as well as a special education program later in his schooling. He may not be capable of independent living as an adult. The primary care physician will be notified of the diagnosis and coordinate further services. The parents are encouraged to attend a parents' support group and consult with experts to learn how their child's full potential may be realized.

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CHAPTER 85

Craniofacial Anomalies

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CASE STUDY

A boy weighing 3,500 g (7.7 lb) is born by normal spontaneous vaginal delivery to a 28-year-old gravida 3, para 3 mother after an uncomplicated term gestation. Apgar scores are 9 and 10. On physical examination, the newborn is well but has an incomplete, left-sided unilateral cleft of the lip and palate.

No other family member has such a deformity, but the mother and father are distantly related. The mother had prenatal care. During the pregnancy she had no illnesses, took vitamins but no other medications, and did not smoke, drink alcohol, or use illicit drugs.

The mother is planning to feed the newborn with formula and wonders if she should do anything special. She is also wondering if her son's lip deformity can be repaired before she takes him home from the hospital. Except for the cleft, the physical examination is normal.

Questions

1. What craniofacial anomalies are common in infants and children?
2. What are feeding considerations in the newborn with cleft lip or palate?
3. What is the appropriate timing of surgery for the more common craniofacial anomalies?
4. What are the major medical problems that children with craniofacial anomalies, particularly clefts of the lip or palate, experience?
5. What is positional plagiocephaly? How is its prevalence related to supine sleeping?

A neonate may be born with a readily apparent craniofacial anomaly, such as cleft lip, cleft palate, or microtia, or anomaly may emerge as an infant ages. The latter includes conditions that may be genetically based but do not manifest until later, such as facial asymmetry (ie, hemifacial microsomia) and premature closure of 1 or more sutures. Alternatively, these anomalies may be environmentally influenced, such as positional or deformational plagiocephaly. *Deformational plagiocephaly* is defined as a condition in which an infant's head and sometimes face are misshapen as a result of prenatal and, in recent years, postnatal external molding, which occur on the infant's malleable cranium.

Epidemiology

The overall prevalence of cleft lip with or without cleft palate is 1 in 1,000 and that of isolated cleft palate is 1 in 2,500 live births. Cleft lip with or without cleft palate is the second most common birth defect in the United States, after Down syndrome, with nearly 7,000 infants with clefts born annually. Racial, ethnic, and geographic variation exists in the prevalence of clefts. For example, the prevalence of clefts in parts of the Philippines is 1 in 200. Similarly, cleft lip with or without cleft palate is most common among Asians and Native Americans (1 in 500) and least common among blacks (1 in 22,500). The sex distribution varies with the type of cleft. Isolated clefts of the palate occur twice as frequently in girls, but clefts of the lip with or without clefts of the palate appear twice as often in boys.

The type of cleft, the sex of the child, and whether a parent or sibling(s) is similarly affected influence the risk for recurrence of clefts in subsequent offspring. Generally, the risk for recurrence of clefts is 4% to 7% for cleft lip with or without cleft palate and 3% for isolated cleft palate.

Clefts may occur as isolated findings or as part of syndromes or sequences. In Van der Woude syndrome, clefts of the lip or palate are associated with lip pits. This condition is inherited in an autosomal-dominant manner and is the most common cause of syndromic cleft lip. Currently, more than 500 Mendelian syndromes are associated with clefts, with approximately 30% of newborns with clefts having other congenital anomalies associated with specific syndromes. Pierre Robin sequence includes micrognathia and glossoptosis (ie, retrodeviated tongue) and a distinct U-shaped cleft. One theory relates the sequence to failure of the fetal neck to extend normally, resulting in compression of the mandible on the chest, thereby restricting its growth and causing malposition of the tongue, thus preventing closure of the palate.

True craniosynostosis occurs in approximately 1 in 2,000 to 3,000 live births, and this prevalence is the same in all ethnic groups. Sex variation exists among the different types of craniosynostosis. Deformational plagiocephaly is reported in 25% to 45% of infants. The term *plagiocephaly* comes from the Greek *plagio,* meaning oblique, twisted, or slanted, and *kephale* for head. Firstborn and male sex increase the risk of deformational plagiocephaly at birth. Most cases of deformational plagiocephaly resolve over time without specific medical intervention.

Microtia is less common and occurs in 1 in 6,000 to 8,000 live births. Other ear malformations, such as auricular dystopia (ie, ear located on the check) or total atresia of the external area, are less

common and can be associated with other syndromes. Other ear anomalies involve protuberant ears (sometimes referred to as "outstanding ears") or pinna with folds or flattened components (eg, antihelix).

Clinical Presentation

Most craniofacial anomalies are readily apparent (Box 85.1). Some anomalies, such as cleft lips or microtia, are noted immediately in the delivery room. Other anomalies, such as craniosynostosis, develop over time. Because the onset of craniosynostosis may be gradual, the parent(s)/guardian(s) may not recognize the condition, which usually appears as asymmetry of the face or skull. Deformational plagiocephaly also evolves over time and is more often noted by the physician rather than the parent or guardian.

The child with craniofacial anomaly may also have medical problems that occur secondary to the deformity. The newborn or infant with cleft palate may present with failure to thrive because of difficulty feeding. The older infant or the child may experience recurrent otitis media, speech impairment, or psychosocial stress. Nasal regurgitation of liquids may occur in the child with obvious palatal cleft or more subtle deformity, such as submucosal cleft of the soft palate.

Pathophysiology

Clefts of the lip and palate (Figure 85.1) are believed to develop as a result of an interruption in the merging of the middle and lateral portions of the face during the sixth to seventh week of gestation. The palate normally closes with an anterior to posterior progression. Any interference with this progression (eg, tumor or encephalocele in the roof of the mouth) leads to a cleft. A vascular disruption may also result in ischemia in the involved areas. Although the etiology of clefts is not fully determined, it is felt to be multifactorial. Multiple genetic risk loci have been associated with nonsyndromic cleft lip with or without cleft palate. The interferon regulatory factor 6 (*IRF6)* gene is consistently associated with nonsyndromic cleft lip and palate. As with other clinical conditions, genetic predisposition interacts with environmental factors to increase the risk of the emergence of a disorder. A newborn with the A2 form of the transforming growth factor-α (*TGFA*) gene is 8 times more likely to have a facial cleft if the mother smokes. Other environmental teratogens associated with clefts include hydantoin, alcohol, warfarin, trimethadione, thalidomide, aminopterin, and topiramate.

Box 85.1. Diagnosis of Craniofacial Anomalies

- Cleft of the lip or palate
- Small, atretic, or malformed ear
- Asymmetry of the face
- Misshapen skull
- Recurrent otitis media
- Speech impairment
- Nasal regurgitation of liquids or foods

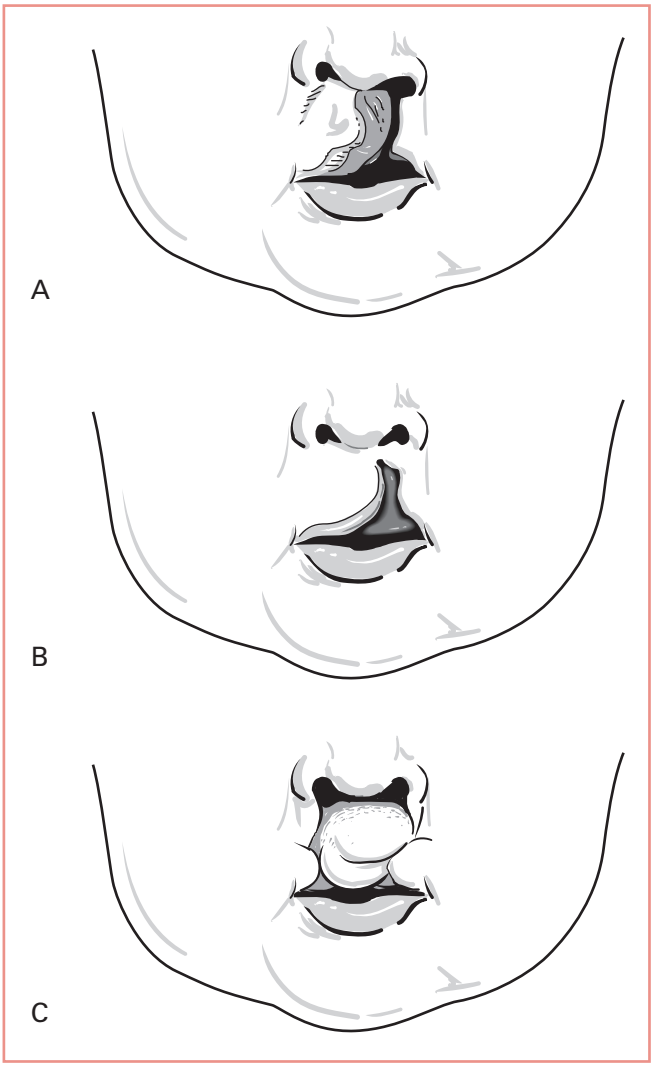

Figure 85.1. Cleft lips. A, Unilateral, complete cleft lip. B, Unilateral, incomplete cleft lip. C, Bilateral, complete cleft lip.

The presence of a cleft palate affects normal oropharyngeal functioning, including sucking and speech. A child may exhibit hypernasal speech caused by the escape of air through the nose and have articulation problems. Recurrent otitis media seems to be related to dysfunction of the eustachian tube.

Facial asymmetry may be the result of hemifacial microsomia either in isolation or as part of a syndrome. Facial asymmetry that is only noted with crying is referred to as "asymmetric crying facies." The condition is present at birth and caused by congenital hypoplasia of the depressor anguli oris muscle (CHDAOM). Although the disorder may occur in isolation, it may also occur in association with other anomalies, including congenital heart disease (40%–50%), head and neck anomalies (45%–50%), skeletal defects (22%), and genitourinary anomalies. Syndromes with which CHDAOM has been associated include CATCH 22, Cayler cardiofacial, VACTERL, and DiGeorge. As with other craniofacial anomalies, the presence of CHDAOM indicates the need for a thorough physical examination for other findings.

Microtia, a small atretic pinna of the ear, results from failure of development of the pinna and portions of the external auditory canal.

It is most likely caused by a vascular accident during the 12th week of gestation. Similar anomalies have been created in laboratory animals by ligature of the stapedial artery. Microtia is considered in the spectrum of branchial arch defects.

Craniosynostosis refers to the premature closure of the sutures, which should remain open until 2 to 3 years of age. The newborn skull consists of membranous bones that meet at the suture lines. The newborn skull is therefore moldable, can change during the birthing process, and can expand in response to growth of the brain. Premature closure of the sutures is a pathologic process. What initiates this pathologic ossification is unclear. Some evidence exists to suggest that skull compression, such as that which occurs in utero with breech presentation or twins, contributes to the process. The presence of other associated anomalies, such as syndactyly, is suspicious for embryologic disturbances in fibrocartilaginous development. Abnormalities in 1 region of chromosome 10 are implicated in syndromic synostosis. Genes associated with fibroblast growth factor receptor have been implicated in some genetic syndromes with craniosynostosis. Any or all of the sutures can be affected, and the closure may result in asymmetry of the skull or microcephaly. Single suture synostosis is classified as simple; multiple synostosis is classified as compound. When closure is related to pathology at the suture, the condition is primary. In the presence of underlying brain pathology, the disorder is secondary. Premature closure of all sutures is often associated with diseases of the central nervous system, with failure of the brain to grow.

Microcephaly may result from premature closure of some or all of the sutures as a primary event or from impairment of the brain and its growth related to some other problem, such as hypoxic encephalopathy or congenital infection. Other disorders involving head size include *macrocephaly*, in which the head circumference is greater than the 97th percentile. Macrocephaly has numerous causes, including hydrocephalus, characterized by enlargement of the ventricular system, and macrencephaly, the latter of which may be caused by enlargement of the brain from anatomic or metabolic conditions, including mucopolysaccharidoses. The child with a large head and who is neurologically normal has *benign* or *idiopathic macrencephaly*. Measuring parental head size is frequently a clue to the correct diagnosis.

Fusion of individual sutures prevents growth of the skull perpendicular to the suture, and skull expansion proceeds in an axis parallel to that of the suture (Figure 85.2). If the sagittal suture fuses prematurely, the head is long and narrow, a condition referred to as *scaphocephaly* ("boat head"). This is the most common type of craniosynostosis, occurring in approximately 54% to 58% of cases of craniosynostosis. If the coronal sutures fuse too soon, the head is flattened; this condition is called *brachycephaly* and occurs in 18% to 29% of cases of craniosynostosis. The prevalence is 1 in 10,000 live births. Unilateral fusion of a coronal suture produces facial asymmetry and a characteristic appearance of the orbit on the affected side, called a *harlequin deformity*, noted on facial radiography. Premature closure of the metopic suture results in the triangular-shaped head characteristic of *trigonocephaly*, reported in 4% to 10% of case of craniosynostosis. Familial cases have been reported, as well as abnormalities of chromosomes 3, 9, and 11. The *FGFR3*P250R mutation has been reported in patients with nonsyndromic craniosynostosis, particularly with coronal or multisuture synostoses.

Premature closure of the lambdoid sutures results in *plagiocephaly* (ie, oblique head) (Figure 85.3). Plagiocephaly may also result from malpositioning in utero or after birth, a condition referred to as nonsynostotic, deformational, or positional plagiocephaly. The skull has been likened to a parallelogram in appearance in cases that also include involvement of the facial structures. Torticollis, which often is attributed to injury to the sternocleidomastoid muscle at birth (see Chapter 119) and abnormal positioning after birth, contributes to plagiocephaly. Plagiocephaly-torticollis sequence occurs in 1 in 300 live births. Malar and contralateral occipital flattening related to preferential positioning by infants are characteristically seen in affected infants. Some affected babies also have hip dislocation or positional talipes (ie, clubfoot) from in utero constraint (see Chapter 113).

Since 1994 with the advent of the Back to Sleep campaign (currently called the Safe to Sleep campaign), the prevalence of positional plagiocephaly has increased significantly, with estimates of between 25% and 45% of infants affected. Most cases are mild and correct over time. Positional plagiocephaly may encompass positional *occipital plagiocephaly* (ie, unilateral flattening of parieto-occipital region, compensatory anterior shift of the ipsilateral ear, bulging of the ipsilateral forehead) and *positional brachycephaly* (ie, symmetric flattening of the occiput, foreshortening of the anterior dimension of the skull, compensatory biparietal widening) or any combination of these 2 deformities. An important strategy to help minimize the development of positional plagiocephaly is to recommend "tummy time," placing an infant in a prone position while awake (eg, with each diaper change) to help develop the muscles of the neck.

Differential Diagnosis

Typically, the differential diagnosis of clefts of the lip and palate presents few problems. Submucosal clefts may be more difficult to diagnose, however. The child with such a cleft may present with recurrent otitis media, hypernasal speech, or nasal regurgitation of liquids. Physical examination may reveal a bifid uvula and occasionally a notch at the junction of the hard and soft palates.

Determining whether any physical finding represents an isolated anomaly or is part of a genetic syndrome may be challenging. Any associated anomalies (eg, syndactyly, atrial septal defect) suggest the possibility of a genetic problem (Boxes 85.2 and 85.3).

Microtia does not present a diagnostic dilemma. The anomaly usually appears sporadically as an isolated condition, although, like a cleft, it may be part of some other syndrome. Microtia is associated with midfacial hypoplasia and antimongoloid slant to the eyes in Treacher Collins syndrome. Microtia may also occur in oculoauriculovertebral dysplasia (ie, Goldenhar syndrome), which is characterized by several associated findings, including hemifacial microsomia (ie, 1 side of the face smaller than the other), epibulbar dermoids, hemivertebrae, microphthalmos, and renal and cardiac anomalies.

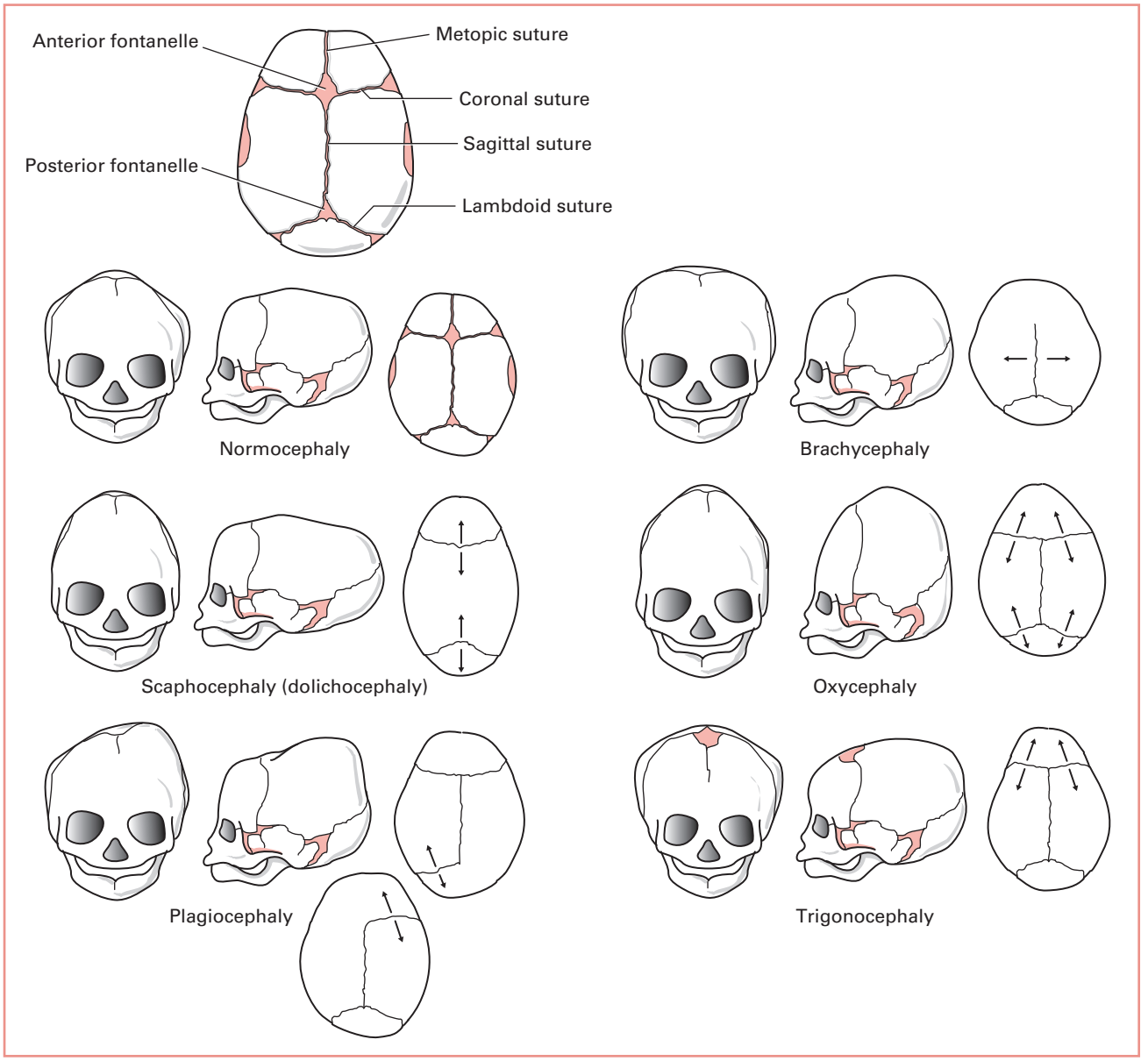

Figure 85.2. Changes in the shape of the skull when sutures fuse prematurely. Growth occurs parallel to the fused suture.

Craniosynostosis may also be an isolated finding or associated with a condition such as Apert syndrome, in which clefts of the palate are also seen (Box 85.4). A careful neurodevelopmental assessment helps determine whether microcephaly is related to an underlying neurodevelopmental disorder. Plagiocephaly may present a diagnostic dilemma: Is the condition related to unilateral craniosynostosis, torticollis, or supine sleeping? A careful assessment of the neck for masses or mobility helps determine the role of the neck musculature in cranial flattening and defines the management approach (eg, neck exercises).

Evaluation

Care must be taken to assess the child and determine if the anomaly is an isolated finding or a component of a syndrome. This information is important in terms of patient care and genetic counseling for the parent(s) on the likelihood of having future offspring with similar anomalies.

History

A medical, family, and psychosocial history should be obtained (Box 85.5). Whether the condition appeared at birth or some time later is particularly significant in lesions affecting the skull, such as craniosynostosis. Maternal use of certain medications, such as diazepam, phenytoin, and isotretinoin (eg, Accutane, Claravis), and alcohol is associated with an increased incidence of clefts of the lip and palate. Maternal smoking also increases the risk of clefting, especially in a genetically vulnerable population. Maternal smoking and high altitude are associated with an increased occurrence of craniosynostosis.

Physical Examination

Height, weight, and head circumference should be measured and plotted at each visit. Head circumference is especially important in the child with craniosynostosis or facial asymmetry. The skull should be palpated to detect perisutural ridging. Inner canthal distance

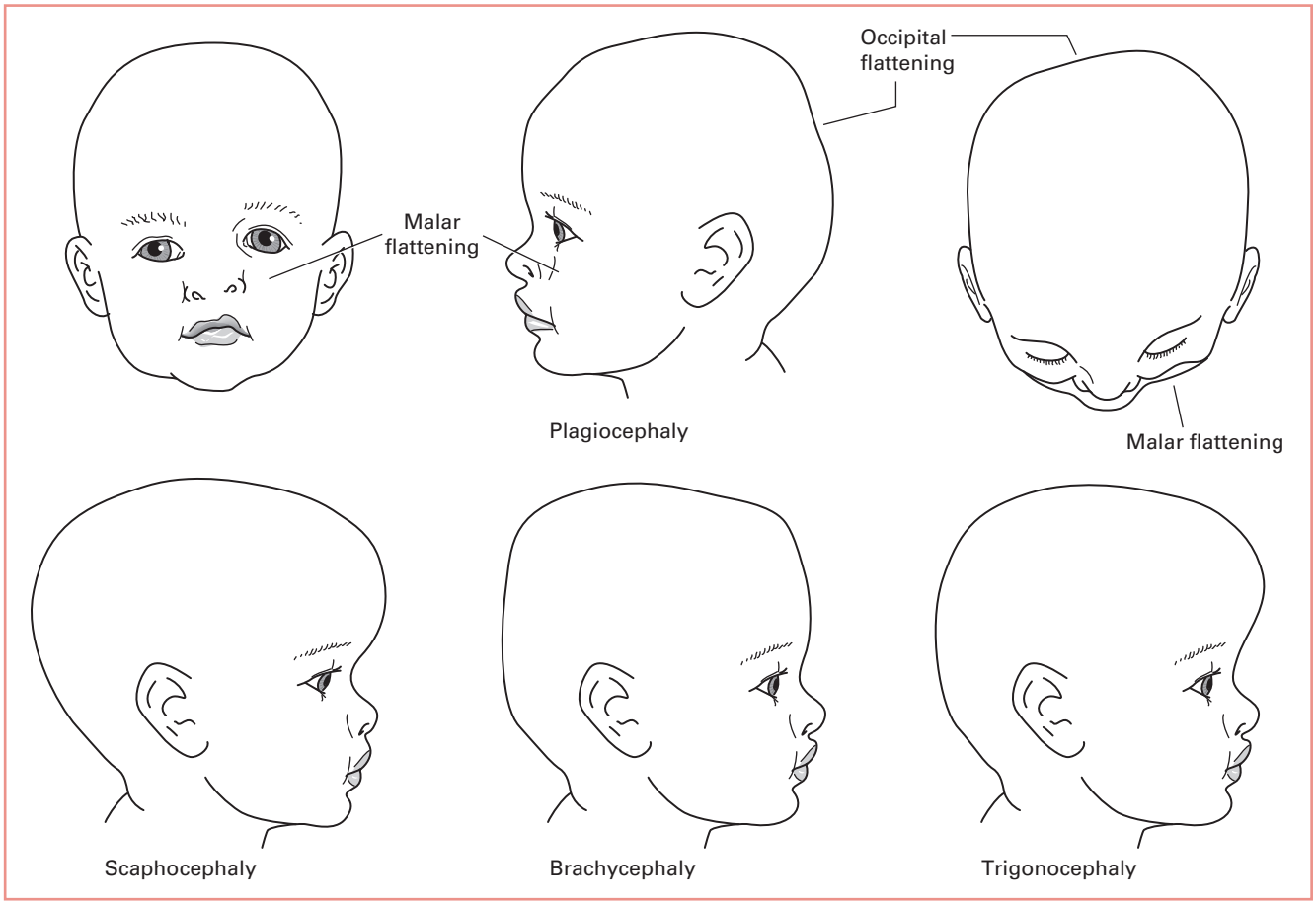

Figure 85.3. **Top row, Classic appearance of an infant with facial asymmetry secondary to plagiocephaly. Bottom row, Classic appearance of infants with craniosynostosis.**

may reveal hypotelorism, a finding that occurs in trigonocephaly. The child's face should be assessed when neutral and when crying or smiling to evaluate the status of the depressor anguli oris muscle. The neck should be palpated for masses and neck range of motion assessed. The growth of the child with craniofacial anomaly must be carefully monitored. Problems with adequate weight gain are frequently experienced by newborns and infants with clefts.

Box 85.2. Genetic Syndromes Associated With Clefts

- Apert
- Ectrodactyly–ectodermal dysplasia–clefting
- Goldenhar (ie, oculoauriculovertebral dysplasia)
- Meckel
- Opitz
- Oral-facial-digital, type I
- Popliteal web
- Stickler (ie, hereditary progressive arthro-ophthalmopathy)
- Treacher Collins
- Van der Woude

Box 85.3. Anomalies Associated With Cleft Lips and Palates

- Anencephaly
- Aniridia
- Ankyloblepharon filiforme adnatum
- Aplasia of trochlea
- Cleft larynx
- Congenital heart disease
- Congenital neuroblastoma
- Congenital oral teratoma
- Foot deformities
- Forearm bone aplasia
- Laryngeal web
- Lateral proboscis
- Nasal glioma or encephalocele
- Oral duplication
- Persistent oropharyngeal membrane
- Polydactyly
- Sacral agenesis
- Spina bifida
- Thoracopagus (ie, conjoined twins)

Box 85.4. Genetic Disorders With Craniosynostosis

- Apert syndrome
- Crouzon syndrome
- Jackson syndrome
- Pfeiffer syndrome

Box 85.5. What to Ask

Craniofacial Anomalies

- What was the birth like?
- Was the delivery vaginal or by cesarean section?
- Were forceps used during the delivery?
- Was the fetus in an abnormal position (eg, breech) in utero?
- What is the child's usual sleeping position?
- Have the findings been present since birth, or did they appear later?
- Has the child experienced other symptoms, such as recurrent ear infections or speech difficulties?
- Does the child have any family history of craniofacial anomalies?
- Does the mother have a history of illness during pregnancy?
- Was the mother exposed to any medications, particularly teratogenic agents, during pregnancy?
- Did the mother use alcohol during pregnancy?
- Did the mother smoke during pregnancy?
- Is the child experiencing difficulties in school (eg, teasing)?
- How is the child performing in school?
- Is development progressing normally? What are the child's milestones?
- Is the child's speech understandable?
- Does the child have any trouble with eating or drinking? Are fluids expelled through the child's nose with swallowing?

The physical examination should focus on defining the extent of the anomaly and determining if associated abnormalities are present. Such abnormalities may involve the face or other parts of the body, including the skeleton. The pharynx should be carefully examined for mobility of the palate. Although some children with nasal regurgitation have a structural deformity, such as a submucosal cleft, others, including infants with DiGeorge syndrome (ie, 22q11 deletion syndrome), have functional impairment with decreased palatal mobility. In the child with microtia, the position of the ear should be noted. When the ear is displaced to the cheek, the condition is called *auricular dystopia.* Cardiac murmur may be noted in the child with cleft, and the murmur should be carefully evaluated.

The child with cleft should be carefully assessed for the presence of otitis media at each visit. Periodic hearing assessments should be carried out in the child with cleft or microtia. Speech and development should also be evaluated.

Laboratory Tests

Routine laboratory tests are not indicated in most children with craniofacial anomalies. Genetic studies are indicated if a genetic disorder is suspected (see Chapter 20). Referral to a geneticist is warranted to ensure testing for recently identified gene associated with craniofacial conditions and for genetic counseling with the parent or parents.

Imaging Studies

Radiographs and imaging studies may be indicated in children with facial asymmetry, microcephaly and macrocephaly, and craniosynostosis. Three-dimensional computed tomography of the skull is particularly helpful in defining which, if any, sutures are fused but is not warranted in the child with suspected positional plagiocephaly. Such studies are helpful in differentiating craniosynostosis and deformational disorders that will resolve on their own. Renal ultrasonography may be indicated in the child with microtia or other ear anomaly because of the association between ear and renal anomalies. Renal ultrasonography is usually normal in the child with isolated microtia but is abnormal in approximately 30% of children with auricular as well as other congenital anomalies, particularly when associated with certain syndromes.

Management

The management of the child with craniofacial anomaly usually requires the expertise of a multidisciplinary team, including a pediatrician, plastic surgeon, otolaryngologist, speech pathologist, social worker, psychologist, orthodontist, and prosthodontist. The primary care physician who is not part of the team can receive information about appropriate patient care and follow-up. It is important for the primary care physician to be familiar with the appropriate nomenclature to be able to communicate with consultants. In brief, clefts of the lip are unilateral or bilateral and complete or incomplete. A complete cleft extends into the nares (Figure 85.1). Clefts of the palate may involve the entire palate or be confined to the secondary or soft palate.

Routine well-child care, including monitoring of growth and administration of immunizations, is most important in the treatment of the child with craniofacial anomaly. Some newborns and infants with clefts are slow feeders. Mothers should be told that although breastfeeding can be carried out, it may present unique challenges; however, the compliancy of the breast tissue creates a natural seal for the lip and palate. If difficulties are encountered, consultation with a lactation specialist may be especially helpful (see Chapter 29). Some formula-fed newborns and infants require the use of special adaptive nipples or feeders. A specific cleft palate feeder, which consists of a plastic bottle that allows for compression of the unit during feeding, is available. A soft nipple typically used by a preterm neonate can also be used. Long nipples, such as lamb's nipples, which are used to feed baby lambs, are not routinely recommended because they cause newborns and infants to gag. The newborn or infant who gains weight slowly may need to be given concentrated formula (see Chapter 146).

Hearing and speech should be monitored. Chronic prophylactic antibiotics or the insertion of pressure equalization tubes may be necessary to manage recurrent otitis media (see Chapter 87). Speech

problems require the expertise of a speech pathologist and placement of the child in speech therapy in the community or school.

Surgical correction is indicated for many anomalies. Clefts usually are repaired as staged procedures during the first 2 years after birth. Repair of the cleft lip, the first procedure, is traditionally scheduled when an infant weighs 10 lb and is 10 weeks of age and the hemoglobin is 10 (ie, rule of 10s). Infants, particularly those with widely separated complete bilateral clefts, may require taping or a prosthetic device to bring tissues in close proximity before surgery is attempted. Appropriate weight gain is therefore critical to ensure timely surgery. If skilled anesthesiologists and nurses are available, cleft lip repair can be carried out within the first 2 weeks after birth. Early repair is recommended at some centers. Repair of the cleft palate, the second procedure, is usually undertaken when the child is between 12 and 18 months of age. Better speech develops with earlier palatal repair. Surgical correction of clefts does not alter a child's propensity to otitis media, although the incidence of otitis media appears to have decreased among children with clefts following the use of conjugated pneumococcal vaccine. The incidence of otitis media decreases as children age, however. Refinement of the cosmetic results, including rhinoplasty, occurs throughout childhood. Orthodontia is frequently a key component to achieve a cosmetically acceptable result and appropriate occlusion of the dentition for speech and chewing. Approximately 10% to 20% of children will develop velopharyngeal insufficiency after repair of a cleft palate. In these cases, the posterior soft palate fails to make a tight seal with the pharynx. A child may experience nasal regurgitation of food or hypernasal speech. Surgical correction of velopharyngeal insufficiency involves lengthening the shortened palate. Additional surgery may also be required for the child with significant jaw deformity. These may include the placement of bone grafts or maxillary advancement.

The child with isolated unilateral microtia often hears, and surgery is recommended to restore a normal anatomic appearance, even if hearing in the affected ear is not improved. Surgical correction of microtia usually is initiated when the child is 5 years of age, before the child starts school. At this time, the ear has achieved 90% of its growth, and the child is spared the potential embarrassment of the deformity in the school setting. Surgical reconstruction can involve the implantation of the child's costal cartilage or a porous polyethylene framework shaped like the pinnae. In either case, several surgical procedures usually are necessary. For the child with other facial anomalies as well, more extensive reconstructive surgery is indicated. The infant with "outstanding ears" may benefit from taping the ears back to the mastoid area early on while the ear cartilage is soft and malleable. Other ear anomalies may be amenable to molds that reshape flattened or folded areas.

Craniosynostosis can be corrected surgically, and such correction is best carried out before 1 year of age. Endoscopic craniosynostosis repair (ie, endoscopic-assisted strip craniectomy) is minimally invasive and requires shorter surgical time (average time, <1 hour) and a reduced length of hospital stay. Discharge can be as early as the first postoperative day. It is the preferred approach in many centers. The age of the infant and the site of the synostosis influence the complexity of the surgical procedure, although a move is afoot to perform endoscopic surgery in infants younger than 16 weeks. Endoscopic strip craniectomy is usually followed by the use of a custom-made molding helmet for up to 7 months. A controversy about whether neurodevelopmental problems are related to craniosynostosis or whether they represent a preexisting condition has arisen. In the developmentally normal child with evidence of closure of all sutures, surgical repair is believed to be warranted. In other cases, the procedure is thought to be reconstructive because it normalizes the appearance of the child with a deformation.

In the newborn or infant with plagiocephaly, when the deformation is believed to be related to torticollis, passive stretching of the neck 5 to 6 times a day (with each diaper change) is used to manage the condition. Additionally, it is recommended that bright objects, such as mobiles, be placed over the child's crib to encourage head turning. Changing the crib position or the position of the newborn or infant in the crib may also encourage movement of the head. Studies have shown that 90% of newborns and infants with congenital torticollis improve with manual stretching. The infant who does not improve with stretching, who has a developmental delay in which the infant does not develop normal neck muscle strength or tone, or who has a deformity that is still present at 6 months of age may benefit from the use of a specially designed helmet or band, referred to as a *dynamic orthotic cranioplasty device,* that reshapes the skull. The device is not used before 6 months of age and generally is worn for a minimum of 4 months.

In an effort to reverse the trend of increasing positional plagiocephaly related to supine sleeping, the American Academy of Pediatrics has recommended that parents and guardians rotate their infant's position when they are awake and allow for tummy time, which is time when the infant is placed prone, sometimes with a rolled receiving blanket under the upper chest. Tummy time can be recommended with each diaper change. This promotes the development of the neck musculature and head control. Most positional plagiocephaly secondary to supine sleeping resolves over time as the infant develops head control and spends less time in a supine position. In 2016 the Congress of Neurological Surgeons released guidelines about the management of positional plagiocephaly that were later endorsed by the American Association of Neurological Surgeons and the American Academy of Pediatrics. These guidelines were based on an extensive review of the existing literature. The guidelines note that imaging studies are rarely indicated. Repositioning of infants is effective, although the evidence supports the use of physical therapy as preferred. Helmets can be used in refractory cases with persistent moderate to severe plagiocephaly. Early initiation of a dynamic orthotic cranioplasty device is usually indicated in the child with developmental delay, including Down syndrome, because of their failure to achieve neuromuscular control that precludes persistent supine posture.

Psychological counseling should be available to affected children and their families to help them adjust to anomalies and the reactions of society. The parent(s)/guardian(s) may be referred to

national agencies and support groups, such as the American Cleft Palate-Craniofacial Association (https://cleftline.org) to help them cope with the potential stress related to giving birth to a child with this anomaly and to advise them about the medical and surgical interventions that are available. FACES: The National Craniofacial Association (www.faces-cranio.org) is another referral source for parents.

Prognosis

Some anomalies, such as deformational plagiocephaly, resolve spontaneously or with exercise and positioning. Most other anomalies can be surgically corrected, leaving little residual evidence of the deformity. School success and psychological well-being may be more resistant to remediation and are highly dependent on the supportiveness of the family and its emotional resources. Children who grow up in settings in which the deformity is thought to be embarrassing have long-term problems with low self-esteem.

CASE RESOLUTION

The newborn has a cleft of the lip and palate. The mother is advised that her newborn can be given formula, and she is given a supply of special feeders. She is also given contact information for a parents' support group and meets other parents of children with similar anomalies. During her visit to the local craniofacial team, she views pictures of children who have undergone a repair and feels relieved.

The mother is advised about the timing of surgery and told that the surgery will be scheduled when the infant is approximately 10 weeks of age. A follow-up appointment in approximately 2 weeks is arranged. Weight gain is monitored, and the adjustment between the mother and the newborn is assessed.

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CHAPTER 86

Common Oral Lesions

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CASE STUDY

A 7-year-old girl is brought to the office for evaluation of a swelling on the inside of her lower lip of 4 to 6 weeks' duration. Her mother reports that it increases and decreases in size. The girl states that the swelling is not painful, and she cannot remember hurting her lower lip. On examination, a raised, bluish, nontender swelling measuring 0.8 × 0.7 cm (0.31 × 0.28 in) is apparent on the mucosa of the lower lip.

Questions

1. What is the differential diagnosis of lip masses and other oral lesions?
2. What laboratory tests or radiologic studies are useful in the evaluation of oral lesions?
3. What management strategies are used to treat cyst-like and other intra-oral lesions?
4. When should children with oral lesions be referred to subspecialists?

Primary care physicians commonly evaluate lesions in the oral cavity. Knowledge of common congenital, developmental, infectious, traumatic, and neoplastic conditions that affect the mouth and its structures can help physicians recognize and manage these lesions appropriately. Although many oral lesions are benign or represent normal variants, others may require specific medical or surgical treatment. Some oral lesions offer clues to underlying syndromic diagnosis, indicate more serious infectious or systemic disease, or occur as side effects of certain medications.

Epidemiology

Oral pathology is common and covers a broad range of lesions. Benign oral lesions, such as gingival cysts, occur in approximately 75% of newborns. Approximately 20% of the population has at least a small *torus palatinus*, a benign bony overgrowth of the palate that usually begins in childhood. Ankyloglossia, commonly referred to as tongue-tie, affects approximately 5% of newborns. Fissured tongue affects approximately 2% of the population. Fissured tongue may be associated with benign migratory glossitis (ie, geographic tongue), which occurs in approximately 1% to 2% of children. Tobacco-associated keratosis occurs at the site of habitual placement of snuff or chewing tobacco and is estimated to affect more than 300,000 children in the United States. Leukoplakia, a premalignant condition associated with smokeless tobacco, occurs in approximately one-half of users. Although the resulting oral cancer is often diagnosed in the sixth or seventh decade of life, the habit of oral tobacco use typically starts in childhood—typically between 9 and 16 years of age. Among US high school students surveyed in 2017, 5.5% report current use of a smokeless tobacco product; use is higher in boys than girls and in whites as well as American Indians/Alaska Natives relative to other racial/ethnic groups.

Aphthous ulcers, commonly known as canker sores, are among the most common oral lesions in developed countries, with typical onset early in childhood. Approximately 20% to 25% of the US population experiences recurrent aphthous stomatitis (RAS). Oral lesions resulting from infections are also common. Approximately 35% of newborns and young infants develop oral candidiasis, commonly known as thrush. Oral herpes lesions are also common and are caused by human herpesvirus, usually type 1. By young adulthood, more than 50% of US individuals are seropositive for human herpesvirus 1. Approximately 20% to 40% of the population has experienced oral herpes at least 1 time.

Chronic ("ordinary") gingivitis usually has its onset in the peripubertal age group, and it ultimately affects as many as 90% of adults. Smoking is a major risk factor for gingivitis and its sequelae–periodontal disease. In 2017, 20% of high school students reported current use of a tobacco product.

Clinical Presentation

Oral lesions may come to the attention of the physician in any number of ways. Some may be obvious at birth, such as a congenital epulis (also called congenital granular cell tumor), which typically presents as a mass arising from the maxillary alveolar ridge and protruding from the oral cavity in a neonate, potentially interfering with breathing or eating. Oral lesions may be an incidental finding on physical examination. For example, in examining a newborn, the pediatrician may notice small (approximately 2–3 mm in size) yellow-white papules along the palatal midline and can reassure the family that these are Epstein pearls, common lesions of no clinical significance. Most oral vascular malformations are present at birth, become more noticeable over time, and rarely regress. One of 3 vessel types usually predominates in such malformations: arterial, venous, or lymphatic. Microcystic lymphatic malformations often affect the tongue and surrounding soft tissue, can be friable, may interfere with eating and speaking, and can result in overgrowth of adjacent bones. When these lesions become infected, they rapidly enlarge and may compromise the airway.

The physician or parent/guardian may be the first to notice thrush. The incidence of oral candidiasis peaks around the fourth week after birth; thrush is uncommon in infants older than 6 to 9 months. Thrush can occur, however, at any age in predisposed patients (ie, immunosuppressed or deficient) and can affect the esophagus as well as the oropharynx. *Candida albicans* in combination with contact irritation has been implicated in *angular cheilitis*, which appears as crusty or scaling erythematous fissures at the corners of the mouth. Other benign oral lesions, such as benign migratory glossitis, are brought to the attention of the physician because parents or guardians are concerned that they represent pathology; however, reassurance is appropriate.

Concerns for ankyloglossia may arise when a newborn has difficulty breastfeeding, particularly when the mother has persistent pain or trauma to her nipple with breastfeeding. Clinically significant ankyloglossia interferes with an effective latch and with normal tongue movement needed to efficiently transfer milk from the breast. Anterior ankyloglossia refers to a sublingual attachment to the underside of the tongue that is close to the tongue tip. In posterior ankyloglossia, the sublingual attachment is farther back on the tongue underside, but it still restricts motion of the tongue. The maxillary labial frenulum can appear quite prominent in infants and young children; however, it usually becomes much less obvious by the time the permanent central incisors erupt.

Physicians may be the first to note swollen, friable, erythematous gingiva along with plaque buildup on and between the teeth representing the initial presentation of chronic gingivitis. Chronic gingivitis is the first and only reversible stage of periodontal disease. Onset is typically in peripubertal children. Although young children experience gingivostomatitis from other causes, they do not usually harbor *Actinobacillus actinomycetemcomitans* or *Porphyromonas gingivalis* and thus do not commonly experience chronic gingivitis or periodontal disease.

Thickening of the mucosa, usually in the labial vestibule, offers clues to smokeless tobacco use. The severity of tobacco-related oral lesions demonstrates a dose-response relationship with the amount, frequency, and duration of smokeless tobacco exposure. *Tobacco-associated keratosis* is a predictable lesion that manifests as an area of thickening at the site of habitual placement of snuff or chewing tobacco. Chronic exposure to smokeless tobacco can result in the development of opaque-white to yellow-brown lesions with a wrinkled appearance, known as leukoplakia and which is considered to be a premalignant condition.

Recurrent oral mucosal trauma, such as habitual biting of the inside of the lip or recurrent irritation from orthodontics, can induce oral lesions anywhere in the mouth but most often does so on the buccal or labial mucosa. One such lesion is a *mucocele*, which is a saliva-filled cyst that is usually less than 1 centimeter in diameter, round, painless, and opaque white or slightly blue in color. *Pyogenic granuloma* is another lesion that can occur at a site of recurrent mucosal or skin irritation. These lesions are blood red or reddish-brown, and they bleed easily. Although they can be protuberant and look scary to parents/guardians, both mucoceles and pyogenic granulomas are benign.

Other oral lesions may present in conjunction with other symptoms. Acute onset of "strawberry tongue," indicating glossitis, often occurs with scarlet fever or Kawasaki disease. The initial herpes simplex virus oral infection–primary herpetic gingivostomatitis–which typically affects infants and young children, is characterized by multiple oral vesicular or ulcerative lesions, fever, malaise, cervical lymphadenopathy, and decreased oral intake. Reactivation of prior human herpesvirus 1 infection often affects the vermillion border of the lip, which is known as *herpes labialis*. Oral lesions may also indicate underlying serious systemic illness, such as Crohn disease, systemic lupus erythematosus, or acute myelogenous leukemia.

Some life-threatening, rapidly progressive infections begin in the mouth. *Ludwig angina* (see Chapter 89) is a painful, rapidly progressive, infectious process of the submandibular space, often presenting as induration and swelling of the floor of the mouth, neck swelling, a superiorly and posteriorly displaced tongue, difficulty swallowing, and subsequent airway obstruction. Ludwig angina is a potential complication of a dental infection; in children, however, Ludwig angina can occur without a clear etiology, or it can complicate oral trauma or gingivostomatitis. *Vincent infection* or *acute necrotizing ulcerative gingivitis* is painful, edematous, bleeding gums with ulcers, necrosis, and pseudomembrane formation in affected areas. When this spreads to the pharynx and tonsils, the condition is referred to as Vincent angina (also called trench mouth). Like Ludwig angina, Vincent angina can progress to life-threatening airway obstruction.

Some genetic syndromes are first detected because of oral lesions. For example, lip pits or mounds in conjunction with cleft lip and/or cleft palate are virtually pathognomonic of Van der Woude syndrome, an autosomal-dominant cause of orofacial clefting. Hyperpigmented lesions (brown or dark blue, similar to freckles) on the lips or buccal mucosa may provide a clue in the diagnosis of Peutz-Jeghers syndrome, an autosomal-dominant condition of multiple intestinal hamartomas. Patients with Peutz-Jeghers syndrome may experience recurrent abdominal pain, intestinal obstruction, or bleeding, and have a 15-fold increased risk of intestinal cancer.

Pathophysiology

Neonatal and Other Developmental Lesions

Gingival cysts in the neonate include Epstein pearls, Bohn nodules, and dental lamina cysts; these are caused by entrapment of tissues during embryologic development. Congenital epulis of the newborn is a rare, gingival tumor of unclear etiology that occurs more commonly in the maxilla than the mandible, with female predilection (8:1), and may occur as a single tumor or multiple tumors. The etiology of fissured tongue and geographic tongue are unknown. Fissured tongue tends to cluster in families, suggesting a genetic etiology, and can also occur in Down syndrome. Benign migratory glossitis results from the loss of the tiny fingerlike projections, called papillae, on the surface of the tongue, giving the tongue a map-like appearance. The inciting factors responsible for oral vascular malformations are

not well understood. Ankyloglossia is thought to result from a localized failure of apoptosis.

Traumatic

Some of the most common oral lesions noted on physical examination result from minor accidental self-bites to the lip or buccal mucosa. Most of these lesions resolve quickly, but recurrent trauma may result in pyogenic granuloma or fibroma formation. A mucocele results from traumatic rupture of a minor salivary gland with subsequent cyst formation.

Infectious

Although an infectious etiology to aphthous ulcers has been proposed, their true etiology remains unclear. Oral herpes lesions usually are the result of infection with human herpesvirus 1. Herpangina results from coxsackievirus A infection. *Candida albicans* causes oral candidiasis. Thrush occurs when normal host immunity is immature (as in neonates) or suppressed (eg, during steroid treatment) or when normal flora is disrupted (eg, while on antibiotics). Newborns may be colonized with *C albicans* during birth. Other sources of transmission to neonates include colonized maternal skin in contact during breastfeeding, pacifiers, and bottle nipples.

Chronic gingivitis occurs after buildup of bacterial plaque on the teeth, adjacent gingiva, and pockets between teeth and gums. Bacteria within plaque release toxins that cause an inflammatory response; the most commonly involved species are gram-negative anaerobic bacteria, including *A actinomycetemcomitans* and *P gingivalis*.

Both Ludwig angina and Vincent infection/angina result from polymicrobial infection, including anaerobes.

Other

Drug-induced gingival hyperplasia can occur in patients taking corticosteroids, phenytoin (most common cause in children), cyclosporine A, or nifedipine. It results from fibrous tissue overgrowth but, much like ordinary gingivitis, is exacerbated by poor oral hygiene and presence of plaque.

Differential Diagnosis

Age at onset, location and characteristics of the lesion, and accompanying signs and symptoms often help narrow the differential diagnosis. The appearance of 1- to 3-mm cysts in the mouth of a neonate is indicative of Epstein pearls, which are the most common and usually are present along the palatal midline; dental lamina cysts, which usually are located bilaterally along the crest of the dental ridge about where the first molars typically erupt; or Bohn nodules, which are found on the buccal and lingual aspects of the ridge, away from the midline. A protuberant mass from the anterior maxillary ridge of a newborn should prompt suspicion for a congenital epulis; however, examination by a pathologist after resection is important to confirm the diagnosis. A mucocele is a painless, clear or bluish, fluid-filled cyst that results from damage to the salivary duct, resulting in extravasation of mucus from the gland into the surrounding soft tissue.

White plaques involving the buccal, lingual, and palatal mucosa are suggestive of oral candidiasis. Thrush can sometimes be confused with milk remaining in the child's mouth after feeding. Scraping the lesion to determine if the white substance is readily removed (as milk is) helps differentiate this from oral candidiasis, in which the white plaques do not easily scrape off; additionally, after scraping, the base of the thrush lesion may be erythematous or may bleed. Some infants and young children have a white coating to the tongue as a normal variant. The lack of white patches on other mucosal surfaces should call into question the diagnosis of thrush. In fissured tongue, grooves that vary in depth are noted along the dorsal and lateral aspects of the tongue.

In scarlet fever, the tongue initially has a white coating overlying the red swollen papillae of the tongue—the "white strawberry tongue," which desquamates at approximately day 4 or 5 of illness, leaving the "red strawberry tongue." In Kawasaki disease, initial presentation usually includes a bright red strawberry tongue and red, dry, cracked lips. Other clinical features and select laboratory testing help differentiate Kawasaki disease from scarlet fever. Both Kawasaki disease and scarlet fever require specific treatment to avoid long-term complications. For scarlet fever, treatment is with penicillin to avoid rheumatic fever, and for Kawasaki disease, treatment is with intravenous immunoglobulin to prevent coronary artery aneurysms.

Common oral ulcers include aphthous ulcers, herpes gingivostomatitis, and herpangina. Oral herpes may be characterized by multiple vesicular lesions, which, after rupture, appear as ulcers involving the lips, skin around the mouth, tongue, and mucosal membranes, typically in the anterior portion of the mouth. The initial infection may occur between 1 and 3 years of age. Aphthous ulcers also involve the anterior mouth, typically along the wet vermillion; however, they usually first appear at a somewhat older age (ie, in the preschool years or later) and with fewer lesions than oral herpes. Factors that may predispose to the development of RAS include familial tendency, trauma, hormonal factors, food or drug hypersensitivity, immunodeficiency, celiac disease, inflammatory bowel disease, and emotional stress. Herpangina may present similarly to herpes, but it more typically involves the posterior pharynx and the palate. Similar lesions on the hands or foot, as in hand-foot-and-mouth disease, may lend support to coxsackievirus A as the etiology.

Trauma to the salivary duct may result in a mucocele. In contrast, a *pyogenic granuloma* is an erythematous, nonpainful, smooth or lobulated mass that often bleeds easily when touched, whereas a fibroma is a moderately firm, smooth-surfaced, pink, sessile or pedunculated nodule, usually noted on the buccal mucosa in the occlusal plane. When located on the gingiva, a pyogenic granuloma can be confused with a *periapical abscess*, which is an erythematous, pus-filled cyst that occurs when infection spreads from the root of an infected tooth to surrounding tissues (also called a gum boil or a parulis). If the abscess ruptures, it often leaves a periapical fistula.

Erythematous and friable gums often indicate the presence of chronic gingivitis. Typically, plaque is seen on and between the teeth. In contrast with plaque-associated chronic gingivitis, which

is usually painless or only mildly uncomfortable, acute necrotizing ulcerative gingivitis (Vincent infection) is quite painful, acute in onset, and associated with ulcers, necrosis, and pseudomembrane formation in affected areas. Swollen and inflamed gingiva can be presenting signs of leukemia in an ill-appearing child with an abnormal complete blood count.

Evaluation

History

The history is very important in evaluating oral lesions and determining the need for further treatment or referral. Key factors to include in the history are age at onset, duration, inciting factors, other medical problems, medications, tobacco use, family history, ill contacts, and associated or systemic symptoms and signs, such as fever (Box 86.1).

Physical Examination

Physical examination of the oral structures should start with the lip (dry and wet vermillion) and surrounding skin (the "white lip"). The examination should then turn to the mucosa, gingiva, teeth, and palate; all aspects of the tongue (ie, superior, inferior, both sides); sublingual structures; frena; and posterior pharynx. The physician should note the number, size, location, and characteristics of the lesions, because this information can be helpful in narrowing the differential diagnosis. The presence and duration of fever should be ascertained. The rest of the body should be examined with specific attention to the presence of other lesions, rashes, lymphadenitis, or arthritis.

Anterior ankyloglossia may be obvious because of a notched or heart-shaped tip of tongue. In more severe cases, the tight and short sublingual frenum makes it difficult to pass a finger under the tongue. Difficulty lifting the tongue to the middle of the mouth and/or difficulty extruding the tongue past the gingiva are other characteristics suggestive of anterior or posterior ankyloglossia.

Laboratory Tests

In otherwise healthy children who present with oral ulcerative lesions, supportive care is typically implemented without pursuing a definitive etiology. If a specific diagnosis is required, human herpesvirus and coxsackievirus can be identified and differentiated with polymerase chain reaction testing. Likewise, oral candidiasis in an otherwise healthy infant usually is managed without diagnostic tests. However, a potassium hydroxide 10% microscopic slide preparation of scrapings from the lesion should demonstrate the characteristic spherical budding yeasts and pseudohyphae. An excisional biopsy or resection may be necessary to determine histology and diagnosis of other oral lesions.

Laboratory tests, including a complete blood cell count, may be helpful in the initial evaluation of the ill-appearing child with oral lesions or in cases in which serious infection, systemic illness, or inflammatory conditions are suspected.

Box 86.1. What to Ask

Common Oral Lesion

- How long has the child had the lesion?
- Is the lesion painful?
- Did the child recently injure the affected area?
- Has the child had any fever?
- Is the child eating as usual?
- Does the child have any other lesions?
- Is the child currently taking any medications? Has the child recently taken any medications?

Imaging Studies

Imaging studies are not indicated in the evaluation of most oral lesions unless the lesions are related to problems of dentition, such as a periapical abscess, in which case radiographs are usually obtained by the dentist rather than the physician. Magnetic resonance imaging may be used for evaluation of oral vascular malformations.

Management

Many of the common oral lesions are developmental or normal variants or are self-limited, and management entails observation to ensure the lesions follow their expected course. For example, gingival cysts in newborns typically regress spontaneously. Oral lesions such as torus palatinus or benign migratory glossitis do not require treatment. Although human herpesvirus 1 gingivostomatitis is self-limiting, primary infection can cause considerable pain and result in decreased oral intake. Early (within 72 hours) antiviral therapy in the form of acyclovir 5 to 10 mg/kg/dose 5 times per day for 7 to 10 days has been shown to shorten the duration of fever, lesions, and odynophagia. Other oral lesions respond well to supportive care. For example, a child with herpangina may benefit from regular ibuprofen or acetaminophen; topical application of a 1:1 mixture of attapulgite (eg, Kaopectate, Donnagel) and diphenhydramine elixir (eg, Benadryl) to form a protective coating over the lesion; avoidance of acidic beverages, such as orange juice, that may cause pain on contact with the ulcers; and close attention to fluid intake and signs or symptoms of dehydration. Amlexanox 5% oral paste or triamcinolone acetonide dental paste reduces pain associated with, duration of, and size of aphthous ulcers and is used in adults with RAS; however, safety of these treatments in children has not been established. Viscous lidocaine has been associated with systemic absorption and subsequent dysrhythmia or seizure and should not be used in children.

Complicated vascular and lymphatic malformations of the oral cavity require specialty consultation with a team experienced in the care of these lesions. Unlike infantile hemangiomas, complicated vascular malformations usually do not involute. Typically, surgical resection is the treatment of choice for lymphatic malformations; however, microcystic lymphatic malformations are difficult to remove and may recur even after resection. Sclerosing therapy and laser treatment are options in some cases. Supportive care includes

treatment with antibiotics when the lesion becomes infected as well as ongoing, aggressive preventive oral hygiene.

Other oral lesions require specific therapy. Thrush is typically treated with nystatin suspension (100,000 units/mL) as 1 mL swabbed to lesions 4 times per day until lesions are resolved. It is important to consider the possibility of an underlying immunodeficiency when thrush occurs outside of infancy or without a reasonable explanation. Angular cheilitis can be managed with nystatin cream or ointment and a low-potency hydrocortisone cream. Some oral lesions, including congenital epulis, mucocele, pyogenic granuloma, and fibroma, are best managed with resection.

Treatment of gingivitis should start with ensuring that a child follows a regular home oral hygiene program, including twice-daily toothbrushing with fluoride toothpaste and flossing, and referral for professional dental care. Regular rinsing with a mouthwash containing essential oils (eg, Listerine Ultraclean, Vita-Myr Mouthwash) or chlorhexidine gluconate oral preparation has been shown to decrease plaque and inflammation. The goals of therapy for gingivitis are to reduce clinical signs of inflammation and gingival bleeding and arrest or reduce the risk of progression of the periodontal disease and maintain dentition. Drug-induced gingival hyperplasia requires therapy similar to that for ordinary gingivitis. Additionally, if the causative medication cannot be discontinued or changed, patients can be referred for surgical removal of excess gingival tissue and fitting of a positive-pressure mouth guard to inhibit further tissue growth. Acute necrotizing ulcerative gingivitis should be managed with débridement and penicillin or metronidazole.

Vincent infection should be managed with débridement and penicillin or metronidazole. Ludwig angina requires surgical drainage as well as treatment with broad-spectrum antibiotics covering gram-negative, gram-positive, and anaerobic bacteria (eg, ampicillin, sulbactam). Securing the airway should be prioritized in both Vincent angina and Ludwig angina.

When a woman reports persistent pain or experiences bruising or bleeding of the nipple with breastfeeding, prompt consideration should be given for clinically significant ankyloglossia, either anterior or posterior. Consultation with a lactation consultant is often helpful as a first step when questions arise about whether ankyloglossia is contributing to breastfeeding difficulty. Not all infants with ankyloglossia have difficulty breastfeeding. Systematic review indicates that sublingual frenotomy reduces maternal pain with breastfeeding and increases breastfeeding efficacy. Sublingual frenotomy, which involves incising the sublingual frenum, is indicated when ankyloglossia is interfering with effective breastfeeding. Longitudinal data are insufficient to warrant sublingual frenotomy in infancy as a means to prevent speech problems in later childhood. No research evidence exists to support incising the superior (upper lip or maxillary) labial frenum in infancy to improve breastfeeding, prevent dental caries, or prevent future orthodontic problems. Cosmetic interventions for a prominent superior labial frenum and/or concerns for a diastema should be delayed until after the permanent maxillary (upper) incisors erupt.

Management of oral lesions may require consultation and collaboration with colleagues in dental, oral surgery, otolaryngology, or other subspecialties. The recommended treatment of a congenital epulis is early resection; however, if a large lesion with potential to obstruct the newborn's airway is diagnosed antenatally, it may be necessary to perform an ex-utero intrapartum procedure to establish an airway before interruption of the fetomaternal circulation. If the etiology of a lesion is unclear or if an oral lesion does not follow its expected course, referral is essential to ensure appropriate diagnosis and treatment.

Prognosis

Most oral lesions in children respond to appropriate intervention without residual problems. However, oral lesions can signal the onset of or occur in association with serious systemic conditions. Although uncommon, rapidly progressive polymicrobial infections of oral structures, such as Vincent angina or Ludwig angina, can be life-threatening. Chronic gingivitis represents the first and only reversible stage of periodontal disease, which is the leading cause of tooth loss in adulthood. Because chronic gingivitis has its onset during childhood, physicians can play an important role in the prevention of periodontal disease by promoting oral hygiene early in life. After periodontal disease extends beyond the gums, it is no longer reversible and gradually destroys the bone and tissue that support the teeth, resulting in halitosis and tooth loss.

CASE RESOLUTION

The child seems to have a mucocele. Mucoceles may spontaneously regress; however, if the lesion persists the child should be referred to an oral surgeon or head and neck surgeon for surgical excision of the lesion.

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CHAPTER 87

Otitis Media

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CASE STUDY

An 18-month-old boy is brought to your office with a 2-day history of fever and decreased food intake. He has had symptoms of an upper respiratory infection for the past 4 days but no vomiting or diarrhea. Otherwise, he is healthy.

The child appears tired but not toxic. On physical examination, the vital signs are normal except for a temperature of 38.3°C (101°F). The left tympanic membrane is erythematous and bulging, with yellow pus behind the membrane. The light reflex is splayed, and mobility is decreased. The right tympanic membrane is gray and mobile, with a sharp light reflex. The neck is supple with shotty anterior cervical adenopathy, and the lungs are clear.

The child has a 10- to 15-word vocabulary, and no one smokes in the household.

Questions

1. What are the differences between acute, persistent, and recurrent otitis media?
2. What factors predispose to the development of ear infections?
3. What are the most common presenting signs and symptoms of ear infection in infants and children?
4. How do the treatment considerations differ between acute, persistent, and recurrent ear infections?
5. What are some of the complications of otitis media?

Otitis media (OM) is the second most common reason after well-child care for a visit to the pediatrician and the most common reason for which antibiotics are prescribed for children. An estimated 30 million office visits per year are for the evaluation and treatment of OM in the United States. More than 25% of all prescriptions written each year for oral antibiotics were for the treatment of middle ear infections. Many surgical procedures, such as myringotomy with tympanostomy tube placement or adenoidectomy, were performed on children for treatment of recurrent disease. However, a dramatic decline has occurred in the prevalence of OM from the prepneumococcal conjugated vaccine (PCV) 7 era to the post-PCV13 era, from 9.5% of office visits to 5.5%, respectively, and from 826 per 1,000 children to 387 per 1,000 children, respectively. Despite this decline, the primary care physician must have a good understanding of these pediatric conditions, which remain quite common.

Otitis media can be classified into the following 5 categories: acute OM (AOM), OM with effusion (OME), recurrent AOM, chronic OME, and chronic suppurative OM. It is important to distinguish between each of these entities because their presentation and management differ.

Acute OM (ie, acute suppurative or purulent OM) is the sudden onset of inflammation of the middle ear, which is often accompanied by fever and ear pain (ie, *otalgia*). The clinical findings of inflammation noted on otoscopic examination are bulging of the tympanic membrane (TM), limited or absent mobility of the TM, air-fluid level behind the TM, and otorrhea not resulting from acute otitis externa (Box 87.1). *Otitis media with effusion* or *serous OM* is the persistence of nonpurulent middle ear fluid after antimicrobial treatment following resolution of acute inflammatory signs. Fluid may persist for 2 to 3 months but usually resolves within 3 to 4 weeks in 60% of cases. *Recurrent OM* is defined as frequent episodes of AOM with complete clearing between each episode, although a more specific definition of recurrent OM is 3 new episodes of AOM requiring antibiotic treatment within a 6-month period or 4 documented infections in 1 year. This condition affects approximately 20% of children with a propensity to otitis; such children typically have their first infection at younger than 1 year. *Chronic OME*, which is also known as serous OM, secretory OM, nonsuppurative OM, mucoid OM, and glue ear OM, is characterized by persistence of fluid in the middle ear for 3 months or longer. The TM is retracted or concave with impaired mobility but without signs of acute inflammation. The affected child may be asymptomatic. The child with chronic OME is at increased risk for developing hearing deficits, speech delay, and learning problems. *Chronic suppurative OM* implies a non-intact TM (ie, perforation or tympanostomy tube present) with at least 6 weeks of middle ear drainage.

Epidemiology

The prevalence of OM peaks in children 6 to 24 months of age. An additional smaller peak occurs at approximately 4 to 6 years of age. Otitis media is relatively uncommon in older children and adolescents. The condition is more common in boys than girls.

Several epidemiologic risk factors for OM have been identified, including age younger than 2 years; first episode before 6 months; familial predisposition; siblings in the household; low socioeconomic status; infant not breastfed; altered host defenses (ie, acquired or congenital immunodeficiencies); environmental factors (eg, cigarette smoke); child care attendance; and the presence of

Box 87.1. Components of Acute Otitis Media

Definition

A diagnosis of acute otitis media requires the following:

- A history of acute onset of signs and symptoms
- The presence of middle ear effusion
- Signs and symptoms of middle ear inflammation

Findings on Examination

- The presence of middle ear effusion that is indicated by any of the following:
  - — Bulging of the tympanic membrane
  - — Limited or absent mobility of the tympanic membrane
  - — Air-fluid level behind the tympanic membrane
  - — Otorrhea (not resulting from acute otitis externa)

Derived from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics.* 2013;131(3):e964–e999.

an underlying condition, such as allergic disease of the upper airway, chronic sinusitis, a cleft palate, or other craniofacial anomalies. Children with Down, Goldenhar, or Treacher Collins syndrome and ciliary dysfunction also are at increased risk for OM. American Indian/Alaska Native individuals have a higher incidence of AOM than whites. Otitis media usually occurs during the winter and early spring, coinciding with peaks in the incidence of viral upper respiratory infections (URIs).

Worldwide, OM results in an estimated 50,000 deaths per year in children younger than 5 years because of the complications of chronic suppurative OM. Otitis media is estimated to affect 65 million to 133 million individuals worldwide, 60% of whom experience significant hearing loss. Chronic suppurative OM is a rare entity in developed countries, in which most instances of OM are of the acute presentation or with effusion.

Etiology

In general, 50% to 90% of cases of AOM culture are bacterial, 20% to 50% are viral, and 66% are both. Until the widespread immunization of children with PCV, the causative microorganisms for AOM were *Streptococcus pneumoniae* (25%–50%), non-typable *Haemophilus influenzae* (15%–30%), and *Moraxella catarrhalis* (3%–20%). Other less common causative organisms include group A streptococcus, *Staphylococcus aureus,* α-hemolytic *Streptococcus, Pseudomonas aeruginosa,* anaerobic bacteria, *Mycoplasma pneumoniae,* chlamydia, and *Mycobacterium tuberculosis.* Bullous myringitis has shown a 97% bacterial-positive rate, primarily with *S pneumoniae*, in contrast to the previous belief that mycoplasma was the causative agent in this condition. Respiratory viruses, such as respiratory syncytial virus, adenovirus, rhinovirus, parainfluenza, coronavirus, and influenza (A and B), also play a role. Respiratory syncytial virus, adenovirus, and coronavirus are associated with an increased rate of AOM, with 50% of children with URI caused by these viruses developing AOM; in contrast, only 33% of patients who have URIs caused by rhinovirus, influenza, parainfluenza, or enterovirus develop AOM. The bacterial pathogens causing AOM in the first 6 weeks after birth are essentially the same as those in older children. However, 10.5% of neonates with AOM have gram-negative bacilli.

Currently, approximately 50% of *H influenzae* and 100% of *M catarrhalis* isolated from the upper respiratory tract are positive for β-lactamase, and 15% to 50% (average, 30%) of *S pneumoniae* are not susceptible to penicillin. The mechanism of penicillin resistance among isolates of *S pneumoniae* is associated not with β-lactamase production but with an alteration of penicillin-binding proteins. This effect varies widely by geographic location and results in resistance to penicillins and cephalosporins.

Clinical Presentation

Children with AOM often have a history of fever and ear pain. Associated symptoms include URI, cough, vomiting, diarrhea, and nonspecific symptoms, such as decreased appetite, waking at night, generalized malaise, lethargy, and irritability. Purulent otorrhea with minimal ear pain and hearing loss may also occur and signifies rupture of the TM. Fever occurs in approximately 30% to 50% of patients. Temperatures exceeding 40°C (104°F) are uncommon and are suggestive of bacteremia or another complication. Verbal children may report tinnitus, vertigo, and hearing loss; Bell palsy is a rare finding. Nonverbal children may appear ataxic on physical examination.

Pathophysiology

The most important factor in the pathogenesis of OM is abnormal function of the eustachian tube (Figure 87.1). Eustachian tube dysfunction occurs for 2 main reasons: abnormal patency and obstruction of the tube. Obstruction is functional (secondary to collapse of the tube), mechanical (from intrinsic or extrinsic causes), or both. Functional obstruction or collapse of the eustachian tube is common in infants and young children because the tube is less cartilaginous and therefore less stiff than in adults; the tube is also more horizontal and shorter in infants and young children. Additionally, the tensor veli palatini muscle is less efficient in this age group. Extrinsically, the presence of lymphoid follicles (eg, adenoidal enlargement) or, rarely, tumors surrounding the opening of the tube contributes to reflux, aspiration, or insufflation of nasopharyngeal bacteria into the middle ear. Intrinsic mechanical obstruction of the eustachian tube occurs as the result of inflammation secondary to a URI or allergy in patients older than 5 years. Viral infections may occur up to 6 to 12 times per year in children younger than 3 years. Subsequently, viral respiratory infections contribute to eustachian tube dysfunction, resulting in negative middle ear pressure, which occurs in 75% of children who have viral URIs. The presence of a viral URI enhances the ability of bacterial pathogens to adhere to and ascend from the nasopharynx to the middle ear via the eustachian tube. Viruses also can affect the local host immune response by impairing leukocyte function, exposing receptors for bacteria, and decreasing the effectiveness of the mucociliary escalator (Figure 87.1).

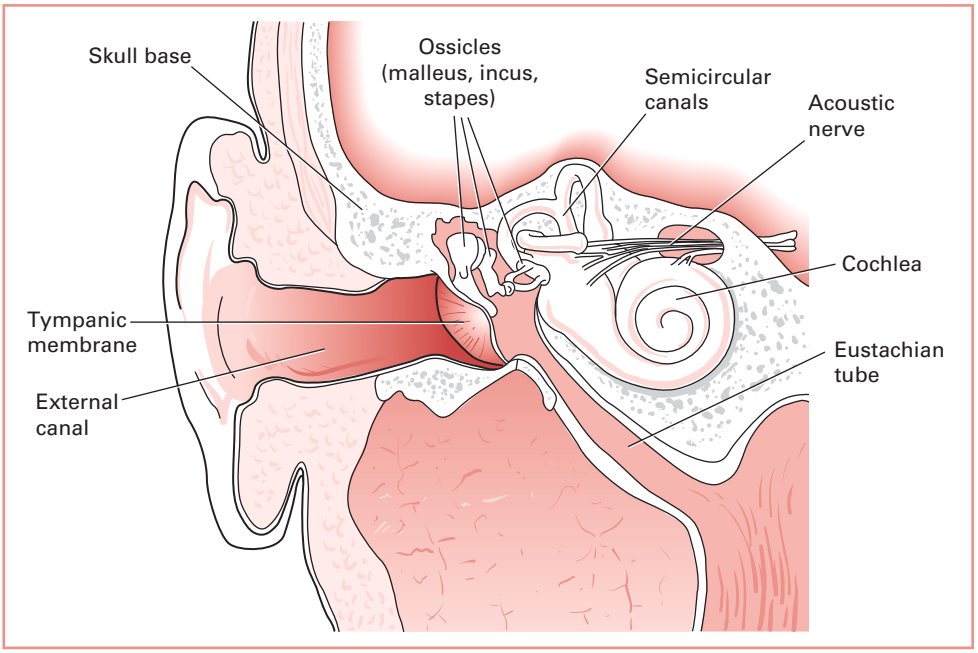

Figure 87.1. Relationship of middle ear to external and inner ears.

Hematogenous spread of microorganisms also can result in OM. Less often, primary mucosal disease of the middle ear from allergies or abnormal cilia contributes to OM.

Differential Diagnosis

The most common cause of otalgia is AOM. Other causes include mastoiditis, which is almost always accompanied by OM; otitis externa; and referred pain from the oropharynx, teeth, adenoids, or posterior auricular lymph nodes. A foreign body in the canal can produce similar symptoms. In the child with ear pain, a search for any of these other conditions must be undertaken if the TM appears completely normal.

Evaluation

History

The history should carefully delineate the symptoms of OM and differentiate from those indicating a more serious condition, such as meningitis (Box 87.2).

For the infant or child with a history of persistent or recurrent OM, it is important to discern when the last documented infection occurred and what treatment, if any, was administered. It is also critical to monitor development, particularly speech.

Physical Examination

To diagnose OM, the TM must be completely visualized and its mobility assessed. Occasionally, this may be difficult because of the presence of cerumen or otorrhea. In such cases, diagnosis is made on the basis of the history, and treatment may be initiated without confirmation by physical assessment. In all other cases, the position, color, degree of translucency, and mobility of the TM are evaluated. Classically, in AOM the TM is full, bulging, hyperemic, opaque, or has an air-fluid level, with limited or no mobility. Typically, the light reflex is distorted or absent. In the case of persistent or chronic OM, signs of inflammation usually are absent and the TM may be retracted, with limited or no mobility. Smartphone apps exist that can be used in assessing the mobility of the TM and can assist in diagnosing OM.

Box 87.2. What to Ask

Otitis Media

- Does the infant or child have fever, ear pain, hearing loss, or otorrhea?
- Is the infant or child inconsolable or lethargic?
- Has the infant or child had a previous ear infection? If so, when?
- Did the child complete the course of prescribed antibiotics?
- How many ear infections has the child had in the past year?
- Is the child taking any medication to prevent recurrent otitis media?
- Does the child attend child care?
- Is the child exposed to passive smoke?
- Is the infant breastfed?
- Does the child seem to hear?
- Is the child's speech development normal?

Associated physical findings with an uncomplicated middle ear infection may include posterior auricular and cervical adenopathy. Other significant findings on physical examination are pain on movement of the pinna, anterior ear displacement, posterior auricular pain, and, rarely, evidence of peripheral facial nerve (ie, seventh cranial nerve) paralysis. The presence of these findings suggests other diagnoses, such as an associated otitis externa or mastoiditis.

Positioning of the infant or young child for evaluation of the ear is critical for an adequate examination. Several methods have been described, including restraining the child on the examination table or allowing parents or guardians to hold the child in their arms or on their laps (Figure 87.2). In the infant, it may be difficult to visualize the TM because the external auditory canal is slightly angulated. Lateral retraction of the pinna may help correct this problem.

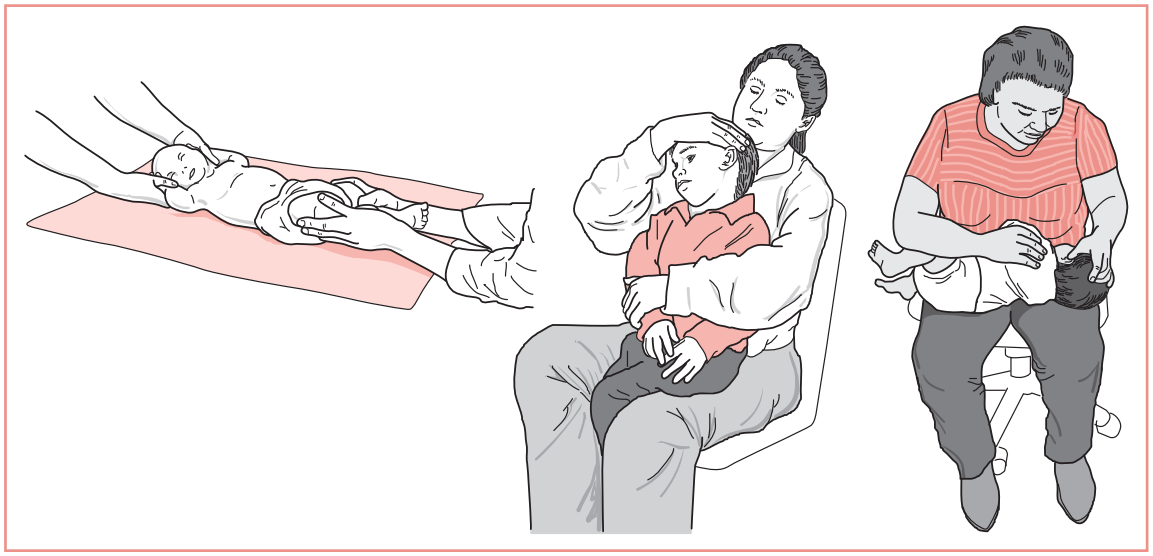

Figure 87.2. Three methods of positioning an infant or child for examination of the ear. Left, Restraining the infant on the examination table. Middle, Holding the child in the arms. Right, Holding the child on the lap.

Laboratory Tests

Although the diagnosis of OM is suspected on the basis of the history and verified on physical examination, tympanometry may be helpful in distinguishing the normal ear from the ear with effusion. In acute cases, audiometry is of limited diagnostic value; however, it is helpful in evaluating the effects of a persistent, recurrent, or chronic middle ear effusion (MEE) on hearing.

Tympanocentesis is the most definitive method of verifying the presence of middle ear fluid and of recovering the organism responsible for the infection. Indications for tympanocentesis or myringotomy are listed in Box 87.3. Nasopharyngeal cultures are not helpful because they do not correlate with middle ear fluid cultures.

Prevention

During infancy and early childhood, the incidence of respiratory tract infections and recurrent OM can be reduced by altering child care center attendance patterns.

Box 87.3. Indications for Tympanocentesis or Myringotomy in the Child With Otitis Media

- Otitis media in the patient with severe ear pain, serious illness, or appearance of toxicity
- Onset of otitis media in the child receiving appropriate and adequate antimicrobial therapy
- Otitis media associated with confirmed or potential suppurative complications, such as facial paralysis, mastoiditis, or meningitis
- Otitis media in the newborn, ill neonate, or immunodeficient patient, in each of whom an unusual organism may be present
- Otitis media in the patient with severe illness in whom second-line antibiotic management has been unsuccessful
- Otitis media in the patient with penicillin allergy in whom the first-line agent was unsuccessful

Immunoprophylaxis with influenza vaccine and PCV has proven effective in reducing the prevalence of OM. Avoiding supine bottle-feeding (ie, bottle propping) and reducing or eliminating pacifier use between age 6 and 12 months, as well as eliminating exposure to passive tobacco smoke, decreases the incidence of AOM.

Breastfeeding, which provides infants with immunologic protection against URIs, other viral and bacterial infections, and allergies, also has a protective effect. Facial musculature may mature differently in breastfed infants, thus influencing eustachian tube function and reducing the risk of aspiration of fluid into the middle ear. Positioning during breastfeeding also has some protective effect, although immune factors in human milk may serve as the most important mechanism for the reduced prevalence of OM.

Increased antibiotic resistance has eliminated the utility of routine antibiotic prophylaxis for recurrent AOM as a means of disease prevention.

Management

In 2013, the American Academy of Pediatrics released clinical guidelines on the management of OM (Box 87.4). One of the perhaps more controversial recommendations was to, depending on the clinical findings in the child between 6 and 24 months of age, not routinely initiate antibiotics but instead observe the child. The American Academy of Pediatrics has not revised these guidelines. Some physicians, based on several subsequent meta-analyses detailing the risk of serious complications, including TM perforation, seventh cranial nerve palsy, subperiosteal abscess, mastoiditis, sinus vein thrombosis, labyrinthitis, bacteremia, and bacterial meningitis, have opted to start antibiotics at the initial encounter.

High-dose amoxicillin is recommended as the first-line treatment in most patients with AOM, although several medications are clinically effective (Table 87.1). The justification for the use of amoxicillin relates to its effectiveness against common AOM bacterial pathogens as well as its safety, low cost, acceptable taste, and narrow microbiological

Box 87.4. Indications for Antibiotics in the Management of Otitis Media

Criteria for Antibacterial Treatment or Observation in the Child with Non-Severe Illness

1. Younger than 6 months: antibacterial treatment
2. Six to 24 months: antibacterial treatment with certain diagnosis or severe illness; observation with unilateral acute otitis media without otorrhea, although a 2015 meta-analysis showed better outcome with antibiotics
3. Two years and older: antibacterial treatment with severe illness or observation in the setting of uncomplicated unilateral or bilateral acute otitis media

Observation is an Appropriate Option if All of the Following Are Present:

A. Caregiver is informed and agrees
B. Caregiver can monitor the child and return should condition worsen
C. Systems are in place for ready communication with the physician, reevaluation, and obtaining medication, if necessary

Adapted with permission from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics.* 2013;131(3):e964–e999.

spectrum. In children with a history of recurrent AOM or who have taken amoxicillin in the previous 30 days, those with concurrent conjunctivitis, or those for whom coverage for β-lactamase-positive *H Influenzae* and *M catarrhalis* is desired, therapy should be initiated with high-dose amoxicillin-clavulanate (90 mg/kg per day of amoxicillin with 6.4 mg/kg per day of clavulanate in a ratio of amoxicillin to clavulanate of 14:1, given in 2 divided doses; this preparation is less likely than other amoxicillin-clavulanate preparations to cause diarrhea).

Alternative initial antibiotics include cefdinir (14 mg/kg per day in 1 or 2 doses), cefuroxime (30 mg/kg per day in 2 divided doses), cefpodoxime (10 mg/kg per day in 2 divided doses), or ceftriaxone (50 mg/kg, administered intramuscularly). Alternative antibiotics vary in their efficacy against AOM pathogens. For example, recent data from the United States on in vitro susceptibility of *S pneumoniae* to cefdinir and cefuroxime indicate efficacy of only 70% to 80%, compared with 84% to 92% amoxicillin efficacy. In vitro efficacy of cefdinir and cefuroxime against *H influenzae* is approximately 98%, compared with 58% efficacy of amoxicillin and nearly 100% efficacy of amoxicillin-clavulanate. A multicenter double tympanocentesis open-label study of cefdinir in recurrent AOM attributable to *H influenzae* showed eradication of the organism in 72% of patients.

For children allergic to penicillin, recent data suggest that cross-reactivity among penicillins and cephalosporins is lower than historically reported. Cross-reactivity is higher between penicillins and first-generation cephalosporins but is negligible between penicillins and second- and third-generation cephalosporins. According to the Joint Council of Allergy, Asthma & Immunology, cephalosporin treatment of patients with a history of mild delayed penicillin allergy (ie, maculopapular or morbilliform eruption after 6 hours of taking penicillin) shows a reaction rate of less than 0.1% to cephalosporin antibiotics and can be prescribed to this subset of patients. This treatment is not appropriate for individuals with severe reaction histories to penicillin (eg, anaphylaxis urticaria, angioedema, bronchospasm, serious delayed reaction [eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, hemolytic anemia]) or uncertain type of reaction where treatment with another antibiotic (azithromycin, clarithromycin, or erythromycin-sulfisoxazole) is recommended.

Currently, tympanocentesis is rarely performed before the initiation of antibiotics. Indications for tympanocentesis include toxic appearance or severe ear pain, because the procedure provides relief through decompression. Tympanocentesis is occasionally performed in a child who has been receiving appropriate and adequate antimicrobial therapy but in whom such treatment does not result in improvement; in the setting of confirmed or potential suppurative complications, such as facial paralysis, mastoiditis, or meningitis; or in the newborn, ill neonate, or immunodeficient patient in whom an unusual organism may be present (Box 87.3).

Table 87.1. Recommended Antibiotics for Initial or Delayed Treatment and for Patients Who Have Failed Initial Antibiotic Treatment

Initial Antibiotic Treatment at AOM Diagnosis or After Observation		*Antibiotic Treatment After 48–72 Hours of Initial Antibiotic Treatment Failure*[a]	
Recommended First-Line Treatments	***Alternative Treatments***	***Recommended First-Line Treatments***	***Alternative Treatments***
Amoxicillin (80–90 mg/kg per day) OR Amoxicillin–clavulanateb (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate)	Cefdinir (14 mg/kg per day in 1 or 2 doses) Cefuroxime (30 mg/kg per day in 2 divided doses) Cefpodoxime (10 mg/kg per day in 2 divided doses) Ceftriaxone (50 mg/kg per day IM or IV for 1–3 days)	Amoxicillin–clavulanate (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate) OR Ceftriaxone (50 mg/kg per day IM or IV for 3 days)	Clindamycin (30–40 mg/kg per day in 3 divided doses), with or without second- or third-generation cephalosporin[b]

[a]If no improvement with second course of antibiotics, consider tympanocentesis and consultation with an otolaryngologist.

[b]May be considered in patients who have received amoxicillin in the previous 30 days or who have the otitis–conjunctivitis syndrome.

Abbreviations: IM, intramuscular; IV, intravenous.

Adapted with permission from Lieberthal AS, Carroll AE, Chonmaitree T, et al. Erratum. The diagnosis and management of acute otitis media. *Pediatrics* 2014;133(2):346–347 DOI: https://doi.org/10.1542/peds.2013-3791.

Adjunctive medications, such as topical analgesics (antipyrine and benzocaine ear drops) and antipyretic agents are important therapeutic options and should be prescribed for the child with significant pain or fever. Antihistamines, decongestants, or steroids have no documented role in the management of OME. Most resolving MEEs that occur after AOM in otherwise healthy children do not need to be treated; the wait-and-watch approach is recommended.

Failure of antibiotic treatment and chronic effusions warrant a referral to an otolaryngologist for further evaluation for pressure equalization tubes, especially if an effusion is present for more than 3 months and associated symptoms, such as vestibular symptoms, school or behavioral problems, ear discomfort, or decreased quality of life, are present. The physician may recommend pressure equalization tubes to manage recurrent OM (3 episodes in 6 months or 4 episodes in 1 year, with 1 episode in the preceding 6 months). Episodes of recurrent OM should be well documented as separate acute infections. Other indications for consultation include hearing loss; any anatomic abnormality, such as a defect of the TM (eg, perforations, cholesteatomas) or intranasal problems (eg, deviated septum, polyp); signs and symptoms of an OM but normal physical examination; and a predisposition to chronic recurrent OM (eg, child with a cleft palate or Down syndrome).

Duration of Therapy

For the child younger than 2 years and any child with severe symptoms, a standard 10-day course of oral antibiotics is recommended. A 7-day course of oral antibiotic appears to be equally effective in children 2 to 5 years of age with mild or moderate AOM. For the child 6 years or older with mild to moderate symptoms, a 5- to 7-day course of oral antibiotics is adequate.

Follow-up of the Patient With Acute Otitis Media

The physician may choose to reassess some children in 10 to 14 days, such as the young child with severe symptoms or recurrent AOM or when specifically requested by the child's parent or guardian.

Persistent MEE is common and can be detected by pneumatic otoscopy (with or without verification by tympanometry) after resolution of acute symptoms. Two weeks after successful antibiotic treatment of AOM, 60% to 70% of children have MEE; this percentage decreases to 40% at 1 month and to 10% to 25% at 3 months after successful antibiotic treatment.

Complications

Complications associated with OM are uncommon with appropriate antibiotic therapy and follow-up. Such complications are either extracranial or intracranial. Extracranial complications include perforation of the TM, conductive and sensorineural hearing loss, ossicular fixation or discontinuity (eg, adhesive OM), cholesteatoma, mastoiditis, petrositis, facial nerve (ie, seventh cranial nerve) paralysis, osteomyelitis of the temporal bone, and Bezold abscess. Intracranial complications are meningitis, extradural as well as subdural abscesses, lateral venous sinus thrombosis, brain abscess, carotid artery thrombosis, and hydrocephalus.

CASE RESOLUTION

The child displays the classic signs and symptoms of AOM: fever, URI, decreased appetite, and an abnormal TM on physical examination. Because of his age and fever and the certainty of diagnosis, he should be treated for 10 days with oral amoxicillin. The prognosis is good given his normal speech development.

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CHAPTER 88

Hearing Impairments

Patricia Padlipsky, MD, FAAP

CASE STUDY

A 15-month-old girl is brought to the office because her parents are concerned that she has not yet begun to speak. The child was the product of a term uncomplicated pregnancy. Her 25-year-old mother, who began to receive regular prenatal care during the second month of gestation, had no documented infections during the pregnancy, took no medications, and denies using illicit drugs or alcohol. The child was delivered at home by a midwife, and a newborn hearing screening was never done. The 27-year-old father is reportedly healthy. The family history is negative for deafness, intellectual disability, and consanguinity.

The child, who is otherwise healthy, has never been hospitalized, but she has had 3 documented ear infections. She rolled over at 4 to 5 months of age, sat at 7 months, and walked at 13 months. She can scribble. The parents report that their daughter smiles appropriately, laughs occasionally, and plays well with other children. As an infant, the girl cooed and babbled, but she now points and grunts to indicate her needs. She does not respond to loud noises by turning her head.

The child's growth parameters, including head circumference, are normal for age. The remainder of the physical examination is unremarkable.

Questions

1. When should deafness be suspected in infants and children?
2. What is the relationship between hearing loss and language development?
3. What are the major causes of deafness in children?
4. Which neonates are at risk for the development of hearing deficits?
5. What methods are currently available for evaluating hearing in infants and children?
6. What are the important issues to address with families who have infants or children with suspected hearing impairment?

Any amount of hearing loss, whether unilateral or bilateral, can cause a significant childhood disability that can compromise speech and language development, academic performance, and social and emotional development. It is essential to identify hearing loss as soon as possible to implement early intervention, which has been shown to prevent many adverse consequences. Children may be born with a hearing deficit (ie, *congenital deafness*), or they may acquire the condition during childhood (ie, *late-onset deafness*). Hearing loss also may be progressive and not identified on early screening. Hearing loss can be classified as conductive, sensorineural, mixed, or auditory neuropathy spectrum disorder (ANSD). Hearing loss is further described by the degree of loss, whether mild (26–40 dB loss), moderate (40–70 dB loss), severe (71–90 dB loss), or profound (>90 dB loss). The most important period for speech and language development is from birth to 3 years of age. Reduced hearing acuity in both ears or even 1 ear during this time can significantly interfere with this important process (see Chapter 33). Therefore, the primary care physician must have a clear understanding of when to suspect impaired hearing in infancy and early childhood and must be familiar with the identification of, evaluation methods for, and treatment options for hearing loss.

Epidemiology

The prevalence of congenital deafness in children is approximately 0.1%. In other words, 1 in 1,000 children is born with severe to profound hearing loss. The prevalence increases to 6 in 1,000 when all degrees of hearing loss, mild to profound, are considered. By age 18 years, it is estimated that 17 in 1,000 children have some degree of permanent hearing loss. This increase over time reflects the addition of patients with progressive, acquired, or late-onset genetic causes. Diagnostic findings for ANSD often are not conclusive in newborns because language skills are still developing and not aberrant at the time of newborn screening.

Prior to the initiation of newborn hearing screening, the average age at diagnosis of most children who were born with hearing impairment was 2 to 3 years. Since the advent of such screening, however, the average age at diagnosis has dropped to 2 to 3 months. Currently, all 50 states have a universal newborn hearing screening as well as early hearing detection and intervention programs. More than 95% of all newborns are screened, and 74% of those found to have hearing impairment have entered an intervention program by 6 months of age. As with any screening program, however, some newborns are missed, especially with at-home births.

Additionally, as many as 40% of identified newborns are currently lost to follow-up, and some forms of early-onset hearing loss are not apparent at birth. Therefore, careful assessment of hearing and language development by the medical professional is essential at each patient encounter.

More than 90% of children with deafness are born to hearing parents. An estimated 20% to 30% of children with hearing impairment develop the condition during childhood. Of these, 70% of children with acquired hearing loss are initially identified by parents rather than physicians. Any concern by parents that their child might have a hearing problem should be taken seriously by the physician and objective testing performed. Risk factors for acquired hearing loss in childhood include persistent otitis media with effusion, history of head trauma, bacterial meningitis, and identification of syndromes or neurologic disorders associated with hearing loss.

Graduates of the neonatal intensive care unit are at significantly increased risk for sensorineural hearing loss (SNHL) and ANSD, with reported rates of SNHL and ANSD of 16.7 and 5.6 per 1,000 infants, respectively, compared with an estimated incidence of ANSD in a well-baby population of 0.06 per 1,000 infants. Diagnostic findings for ANSD often are not conclusive in newborns because language skills are still developing and not aberrant at the time of newborn screening. Associated factors, such as preterm birth (birth weight <1,500 g [<3.3 lb]), hyperbilirubinemia, prolonged mechanical ventilation, extracorporeal membrane oxygenation treatment, perinatal asphyxia, exposure to ototoxic drugs, and neonatal sepsis increase the risk for ANSD. Other factors associated with deafness in childhood include meningitis, parental consanguinity, craniofacial malformations, congenital viral infections, exposure to chemotherapy, and a family history of deafness.

Box 88.1. Risk Factors for Hearing Impairment

- Family history of congenital or early SNHL
- Congenital infection known to be associated with SNHL
- Craniofacial anomalies
- Birth weight <1,500 g (<3.3 lb)
- Hyperbilirubinemia over the exchange level
- Infectious diseases associated with SNHL
- Exposure to ototoxic medications
- Bacterial meningitis
- Low Apgar scores at birth
- Prolonged mechanical ventilation in neonatal period
- Findings of a syndrome associated with SNHL
- Any parental/caregiver concern about hearing, speech, language, or developmental delay
- Head trauma, especially with fracture of the temporal bone
- Neurodegenerative disorders

Abbreviation: SNHL, sensorineural hearing loss.

Clinical Presentation

The newborn may present to the primary care physician having had an abnormal newborn hearing screening test. The initial newborn screening is mandated by 1 month of age, with definite testing by an audiologist for abnormal tests by 3 months of age. Intervention should begin by 6 months. For the infant who passes hearing testing but has positive risk factors for hearing impairment (Box 88.1), communication skills should be assessed at every well-child visit and diagnostic audiologic assessment should be done by 24 to 30 months of age.

In the unscreened population or for children with progressive or acquired hearing loss, parents are often the first to suspect hearing loss. A parent may be concerned that the toddler is indicating needs by grunting and pointing rather than using words or that the child does not seem to respond to sounds. Children with hearing impairments frequently present to physicians with delayed speech or speech impediments; children produce what they hear.

Normal speech volumes range from 30 to 50 dB, whereas typical street traffic volume is approximately 60 dB. Standard telephone rings and shouts are approximately 80 dB, and lawnmowers are approximately 90 dB. Therefore, children with a 50-dB hearing loss may hear their mother when she yells at them and may startle when the telephone rings. However, they do not hear most conversational speech, and they may not always hear the teacher in a classroom, especially if they are not in the front and in the setting of significant extraneous noise. This can result in behavioral problems, such as inattention, temper tantrums, and aggressive play with other children (Box 88.2).

Worsening speech or school performance may herald longstanding or progressive mild-to-moderate hearing loss. Other presentations of mild or progressive hearing loss may consist of either withdrawal from social activities and playing alone or playing the television and music at increasingly loud volumes.

Hearing impairment can be particularly difficult to recognize in infants younger than 6 months because they may have no obvious symptoms of a hearing deficit. They may startle to moderately loud noises and begin to vocalize as other infants do (Figure 88.1). If the history is suggestive of a hearing deficit or a parent or caregiver expresses concern, audiologic testing should be performed.

Box 88.2. Diagnosis of Hearing Impairment in the Pediatric Patient

- Parental concern or suspicion of hearing loss
- Delayed speech and language development
- Associated risk factors, including preterm birth, exposure to ototoxic drugs, congenital or acquired central nervous system infections, family history of hearing loss, and craniofacial abnormalities
- History of behavioral problems or poor school performance
- Abnormal hearing test

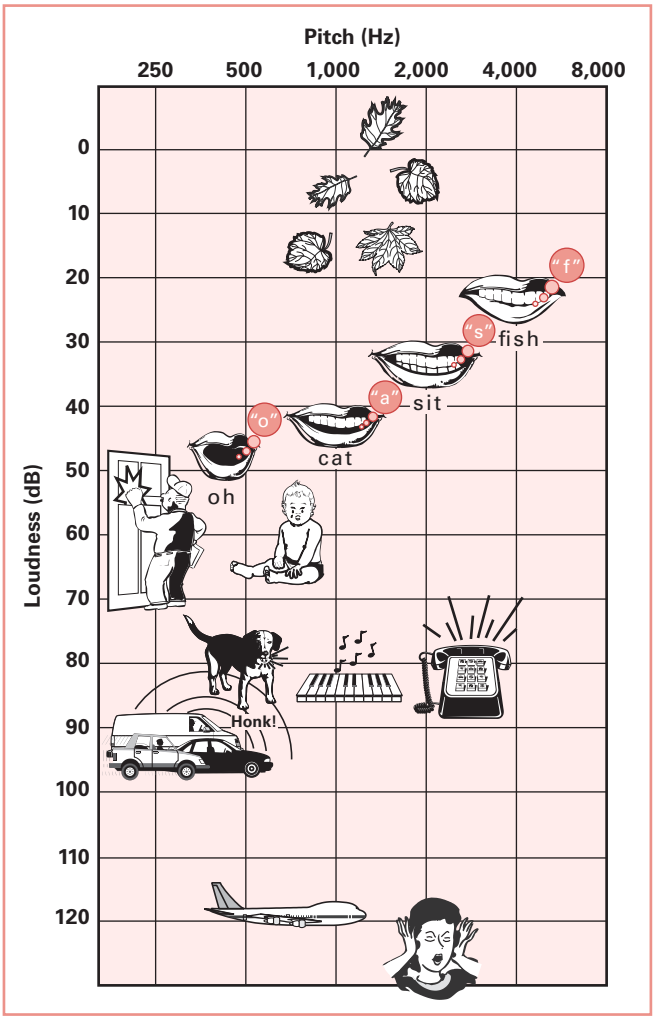

Figure 88.1. **Loudness of everyday sounds.**

Pathophysiology

Mechanism of Hearing

Sounds in the form of pressure waves are carried from the environment through the external auditory canal to the tympanic membrane (TM). These waves are converted to mechanical vibrations by the ossicles, and the mechanical vibrations are then transmitted from the TM to the inner ear, where they are transformed to fluid vibrations. Finally, these fluid vibrations are converted into nerve impulses by nerve endings within the organum spirale located in the cochlea in the inner ear. These impulses are conducted via the auditory nerve to the auditory cortex (Figure 88.2).

Hearing impairments can be classified according to the part of the auditory system affected or by the cause of the hearing loss.

Types of Hearing Loss

A *conductive hearing loss* (CHL) denotes an abnormality from the pinna, external auditory canal, TM, or middle-ear ossicles. Conductive hearing loss can occur in congenital anomalies, such as atresia, impacted cerumen, otitis externa, serous otitis media, otitis media with effusion, TM perforation, ossicular discontinuity, and otosclerosis. An SNHL is an abnormality that affects the cochlea, inner ear, or auditory nerve. Congenital infections, anomalies, genetic disorders, and loud noise result in this type hearing loss. The loss of cochlear function, usually from damage to sensory hair cells in the organum spirale, is the main cause of permanent childhood hearing loss. A *mixed disorder* has characteristics of both conductive and sensorineural losses. In *retrocochlear hearing loss*, the auditory nerve, brain stem, or cortex is affected. This includes ANSD noted in neonates after neonatal intensive care unit stays. In auditory neuropathy, sound enters

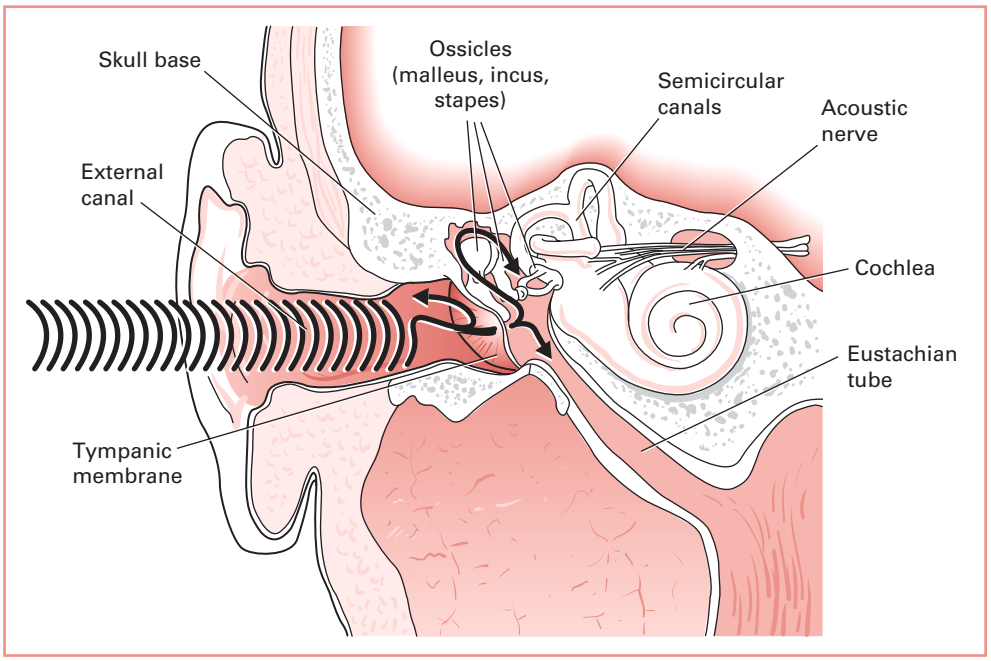

Figure 88.2. **Sound waves (represented by arrows) passing through the external ear into the middle ear.**

the ear normally, but because of damage to the inner ear or the hearing nerve, sound is not organized in a way that the brain can understand.

Etiology of Hearing Impairment

The causes of hearing loss can be broadly divided into genetic and acquired and further divided into congenital and/or progressive (Table 88.1). Of the 1 in 1,000 individuals born with severe to profound hearing loss, the cause is genetic in approximately 50%, nongenetic in approximately 25%, and idiopathic in approximately 25%. Of the 50% with a genetic cause, the hearing loss is syndromic in 30% and nonsyndromic in 70%. More than 500 forms of syndromic hearing loss exist, each with associated clinical features. Most of these syndromes are rare. Waardenburg syndrome is the most common type of autosomal dominant syndrome with SNHL. Usher syndrome and Pendred syndrome with goiter are examples of autosomal recessive syndrome with SNHL. Down (ie, trisomy 21) syndrome and oculoauriculovertebral dysplasia (ie, Goldenhar syndrome) often have associated hearing impairment. Alport syndrome with progressive SNHL and nephritis is also well recognized and is X-linked. Most cases of genetic hearing loss are nonsyndromic, however, and result from a single gene defect encoding connexin 26 protein. This recessive disorder with mutations in the *GJB2* gene accounts for 30% to 50% of all cases of nonsyndromic hearing loss. Genetic malformations of the ear pinnae or ossicles do occur but are the least common cause of hearing loss. Genetic mutations may result in different types of deafness with various presentations and outcomes, that is, hearing loss may be conductive, sensorineural, or mixed and may be static or progressive, with the initial presentation in infancy or later childhood.

Table 88.1. Major Causes of Childhood Deafness

Hearing Loss Type	*Conductive Hearing Loss*	*Sensorineural Hearing Loss*
Congenital	Microtia/atresia Tympanic membrane abnormalities Ossicular malformations	Genetic disorders (eg, syndromic, connexin 26, mitochondrial) In utero infection (eg, cytomegalovirus, measles, mumps, rubella, varicella, syphilis) Anatomic abnormalities of the cochlea or temporal bone Exposure to ototoxic drugs during pregnancy (eg, alcohol, isotretinoin, cisplatin) Hyperbilirubinemia
Acquired	Infection (eg, acute otitis media, otitis externa, ossicular erosion) Otitis media with effusion Foreign body (including cerumen) Cholesteatoma Trauma (eg, ossicular disruption, tympanic membrane perforation)	Infection (eg, bacterial meningitis, measles, mumps, rubella, Lyme disease) Trauma (eg, physical or acoustic) Radiation therapy for head and neck tumors Neurodegenerative or demyelinating disorders (eg, Alport syndrome, Cogan syndrome)

Adapted with permission from Gifford KA, Holmes MG, Bernstein HH. Hearing loss in children. *Pediatr Rev.* 2009;30(6):207–216.

Acquired environmental causes of hearing loss include prenatal, perinatal, or postnatal events and exposures, such as congenital infections, bacterial meningitis, hyperbilirubinemia, complications of prematurity, and exposure to ototoxic drugs. Cytomegalovirus (CMV) likely is the most frequently unrecognized congenital infection causing deafness. Even if an infant is asymptomatic from the CMV infection, a 10% to 15% chance exists that the infant will develop an SNHL. Other congenital infections, such as toxoplasmosis, measles, mumps, rubella, herpes simplex virus, HIV, and syphilis can also cause hearing loss. Hearing loss associated with bacterial meningitis accounts for as many as 20% of cases, with *Streptococcus pneumoniae* as the prevalent responsible organism. The incidence of *S pneumoniae* and *Haemophilus influenza* type b meningitis has decreased tremendously in young children following the advent of conjugate vaccine, and the prevalence of postmeningitic hearing loss has similarly declined. The role of steroids in the management of bacterial meningitis has also contributed to the decrease in SNHL in survivors.

With the recognition and treatment of hyperbilirubinemia in term newborns, hyperbilirubinemia as a cause of hearing loss is now rare in the United States and other developed countries. Preterm birth as a cause of hearing loss is, however, not uncommon. Because of associated complications, preterm newborns have higher rates of severe hearing loss than do term newborns. Some antibiotics (eg, aminoglycosides) and other medications (eg, loop diuretic agents) can be irreversibly ototoxic; other drugs may cause only transient effects.

Any head injury, especially if the injury damages the temporal bone, can cause deafness in children. Fractures through the cochlea and vestibule can result in severe to profound hearing loss, and damage to the TM and/or ossicles can result in a significant CHL. Acoustic trauma (ie, noise-induced hearing loss) from continuous or significant exposure to loud noise can also cause irreversible SNHL. With children's use of personal listening devices, the prevalence of this cause of hearing loss is increasing.

Hearing loss caused by middle ear effusions is the most common cause of childhood hearing loss. It is often not discussed because it is usually considered benign and transient in nature. However, of all ears with resolved otitis media persistent fluid is exhibited in 40% at 1 month, 20% at 2 months, and 10% at 3 months after infection or after the conclusion of treatment. It is important to identify whether this effusion is affecting the child's hearing. Speech development is greatest in the first 3 years after birth and can be affected if a child has chronic effusion that is

causing hearing loss. Any concern for hearing loss warrants objective testing, and consultation with an otolaryngologist should be recommended.

Differential Diagnosis

In addition to hearing loss, communication disorders should be considered in the infant or child with delayed speech and language development. These include problems with speech perception, language comprehension, formulation of language output, and speech production. Unrecognized conditions, such as intellectual disability or autism spectrum disorder, are responsible for some of these disorders. Other etiologies include specific central nervous system deficits as well as impairments of fine motor control of the oropharynx.

Evaluation

Newborn Hearing Screening

The earlier the diagnosis of hearing loss is made, the sooner interventions can be initiated to help the child develop. In 1994, the Joint Committee on Infant Hearing (JCIH), composed of representatives from several professional organizations, endorsed universal newborn hearing screening. The goal was the early identification of hearing loss in newborns and infants before age 3 months and the implementation of intervention services by age 6 months. As a result of these recommendations, states have implemented legislation mandating newborn hearing screening and intervention programs. A subsequent position statement was issued in 2000. The American Academy of Pediatrics endorsed this statement and promoted newborn hearing screening as well as periodic hearing assessment for every child. As a result, hearing screening has been established as an essential newborn evaluation; however, a significant need exists to improve infrastructure to ensure that physicians receive and process screening results. The JCIH policy statement was most recently updated in 2007 and includes more specific guidelines for diagnostic audiologic evaluation, medical evaluation, and surveillance screening in the medical home. Per the policy, all infants and children—regardless of hearing screening results—should undergo ongoing assessment of communication skills beginning at 2 months of age. Any child with evidence of hearing loss in 1 ear or both ears should be offered early intervention. In 2013, a supplement was published to the 2007 JCIH position statement describing principles and guidelines for early intervention after a child is diagnosed with hearing impairment.

History

Because the primary symptom of hearing impairment or deafness is failure to learn to speak at the appropriate age, the most important aspect of the history in the child with possible hearing loss is determining whether speech is developing normally. Even an infant with deafness may begin cooing and babbling in infancy, and these early attempts at verbalization are not useful milestones for assessment of hearing deficits. It helps to ask the parent or guardian whether that individual is at all suspicious or concerned about the child's speech or hearing. Guidelines for assessing language development are found in Table 88.2 (also see Chapter 33). It is also important to assess for risk factors for deafness, such as a positive family history, infection during gestation, history of prematurity, hyperbilirubinemia, neonatal sepsis, and asphyxia (Box 88.3).

Table 88.2. Expected Speech, Language, and Auditory Milestones

Age	*Receptive Skills*	*Expressive Skills*
Birth	Turns to source of sound Shows preference for voices Shows interest in faces	Cries
2–4 months	Turns to source of sound Shows preference for voices Shows interest in faces	Coos Takes turns cooing
6 months	Responds to name	Coos Takes turns cooing
9 months	Understands verbal routines (eg, "wave bye-bye")	Babbles Points Says mama, dada
12 months	Follows a verbal command	Uses jargon Says first words
15 months	Points to body parts by name	Learns words slowly
18–24 months	Understands sentences	Learns words quickly Uses 2-word phrases
24–36 months	Answers questions Follows 2-step commands	Phrases 50% intelligible Builds ≥3-word sentences Asks "what" questions
36–48 months	Understands much of what is said	Asks "why" questions Sentences 75% intelligible Masters the early acquired speech sounds: m, b, y, n, w, d, p, and h
48–60 months	Understands much of what is said, commensurate with cognitive level	Creates well-formed sentences Tells stories 100% intelligible
6 years	Understands much of what is said, commensurate with cognitive level	Pronounces most speech sounds correctly; may have difficulty with sh, th (as in think), s, z, th (as in the, l, r, and s in treasure)
7 years	Understands much of what is said, commensurate with cognitive level	Pronounces speech sounds correctly, including consonant blends, such as sp, tr, bl

Adapted from Feldman HM. Evaluation and management of language and speech disorders in preschool children. *Pediatr Rev.* 2005;26(4):131–142.

Box 88.3. What to Ask

Hearing Impairment

- Does the child seem to respond to sounds?
- Does the child attempt to repeat sounds?
- How does the child indicate his, her, or their desires or needs?
- How are the parent(s)/guardian(s) currently communicating with the child?
- Does evidence exist of a congenital infection, structural anomaly of the head and neck, or syndrome?
- Is there a history of prematurity or other prenatal or perinatal problem?
- Has the child had any serious bacterial infection, such as meningitis?
- Does the child have a history of repeated ear infections or exposure to ototoxic drugs?
- Aside from the hearing problem, is the child developmentally normal?
- Is there a family history of deafness, consanguinity, or multiple miscarriages or stillbirths?

Physical Examination

A complete physical examination should be performed on all children. In particular, any dysmorphic facial features that may be suggestive of a syndrome with an associated hearing deficit should be noted. Other anomalies of the head and neck should be noted as well. Abnormal pigmentary conditions may be important clues. The eyes should be evaluated for heterochromia and hypertelorism findings seen in Waardenburg syndrome, which also includes SNHL. The size and shape of the pinnae and external ear canals should be carefully inspected for abnormalities and patency, respectively. Preauricular pits or tags may be apparent. Additionally, the TMs should be visualized and assessed for the presence of middle ear effusion that may influence subsequent audiologic tests. Insufflation may be helpful in the assessment of middle ear effusion. The oropharynx should be examined for a cleft palate or bifid uvula, which may be associated with a submucosal cleft. The manner in which the child communicates with the parent or guardian should be noted, if possible, and the child should be assessed for response to sound.

Laboratory Tests

Tympanometry does not measure hearing, but it is useful in assessing the presence of middle ear fluid and the mobility of the TM. Tympanometry can be particularly helpful with the uncooperative, crying child in whom assessing the appearance of the TM and insufflation is difficult. Different types of hearing tests for evaluating infants and children for possible hearing deficits are available to the primary care physician (Box 88.4). The 2 tests used for the screening of newborns are otoacoustic emissions and auditory brainstem response (ABR), the latter of which is also referred to as brainstem auditory evoked response. *Otoacoustic emissions* testing measures cochlear function in response to a specific stimulus via a small probe that contains a microphone that is placed in the ear canal. This test can be used for newborn hearing screening in the low-risk newborn. It requires no sedation and is inexpensive and quick; it can be completed in 10 minutes. It has been implemented quite successfully as the hearing screening test in hospitals and primary care physician offices and has the advantage of being useful for all ages. ABR is an electrophysiological measurement of activity in the auditory nerve and brain stem pathways. Electrodes are placed on the head of the newborn, infant, or child to record brain wave activity while a specific auditory stimulus is presented through earphones to 1 ear at a time. Auditory thresholds can be estimated. ABR is used as a screening tool for newborn hearing screening and only takes approximately 10 minutes. As a screening tool, it delivers a preset intensity and frequency. If an infant does not pass the screening test, a full ABR should be done in which different intensities and frequencies are used to help identify the degree of hearing loss and at what frequencies. This evaluation takes approximately 90 minutes. Both otoacoustic emissions and ABR results can be affected by the presence of outer ear or middle ear disease. ABR requires a calm, resting infant. The older infant may require sedation. *Behavioral observation audiometry* measures a child's response to speech and frequency-specific stimuli presented through speakers in a soundproof room. This method of testing assesses hearing in the better ear only and cannot detect unilateral hearing loss. It is used for the child with a developmental age of younger than 6 months. *Conditioned play audiometry*, like *conventional audiometric testing*, measures auditory thresholds in response to frequency-specific stimuli presented through earphones to 1 ear at a time. The patient is instructed to perform a particular task, such as putting a block in a container or raising his or her hand, when the stimulus is heard. The child as young as 3 years can be tested by conditioned play audiometry, and the child age 4 or 5 years can be assessed using conventional audiometric testing. Any abnormal results on these screening tests should be used in conjunction with evaluation by an audiologist and an otolaryngologist. In the case of the high-risk infant, audiologic testing should be repeated at least every 6 months until 3 years of age and at appropriate intervals thereafter, depending on the etiology of the suspected hearing loss and test results.

Box 88.4. Tests for Evaluating Hearing

- Automated auditory brainstem response: used for newborn hearing screening
- Behavioral observation audiometry
- Brainstem auditory evoked response
- Evoked otoacoustic emissions (a newer type of newborn hearing screening)
- Conditioned play audiometry
- Conventional audiometric testing

Diagnostic tests to consider in evaluating the cause of deafness include titers for congenital infections, such as CMV, toxoplasmosis, HIV, and rubella, and fluorescent treponemal antibody absorption tests for syphilis. In the newborn period, a CMV culture may be helpful. Testing for the *GJB2* gene, the mitochondrial A1555G mutation that predisposes an individual to ototoxicity from drugs, and the *SLC26A4* gene for Pendred syndrome, along with CMV testing, would reveal an etiology for 40% of cases of congenital hearing loss and 60% of cases of late-onset hearing loss. Thyroid function tests are necessary if Pendred syndrome is suspected, especially in the school-age child with goiter. Proteinuria and hematuria should also be ruled out by urinalysis, especially in boys with a positive family history of deafness and renal failure, both of which are findings suggestive of Alport syndrome. Electrocardiography is recommended for the detection of conduction defects, such as QT prolongation in Jervell and Lange-Nielsen syndrome.

Imaging Studies

Occasionally, computed tomography or magnetic resonance imaging of the temporal bone may be obtained to view the anatomy of the middle and inner ear, particularly in cases of a suspected cochlear or vestibular malformation or fistula. Necessity for such studies should be determined by an audiologist or otolaryngologist.

Management

According to the 2013 supplement to the JCIH 2007 statement, "Screening and confirmation that a child is deaf or hearing impaired are largely meaningless without appropriate, individualized, targeted and high-quality intervention. For the infant or young child who is deaf or hard of hearing to reach his or her full potential, carefully designed individualized intervention must be implemented promptly, utilizing service providers with optimal knowledge and skill levels and providing services on the basis of research, best practices, and proven models." Studies have shown that the earlier a hearing deficit is detected and remediation begun in an otherwise normal newborn, the greater the likelihood the child will have language development close to that of a hearing child. Initiation of intervention before 6 months of age contributes to infants being able to develop language as well as social and emotional skills appropriate for their age. School performance and communication skills have been shown to be better in those identified at a younger age. It appears as though the critical period for hearing and speech development is from birth to 3 years of age. All newborns, infants, and children identified with a hearing deficit should be referred to an otolaryngologist and audiologist for immediate assessment and recommendation for assistive devices.

If a child is diagnosed with bilateral otitis media with effusion, recent guidelines indicate that a hearing test should be done if the effusion lasts for 3 months or longer. If a hearing loss is identified, tympanostomy tubes should be inserted.

Additional assessment for the child with identified hearing loss includes an ophthalmologic evaluation and referral to a geneticist. After an infant or child is found to have a hearing impairment, careful follow-up is necessary so that any further reduction in hearing is promptly identified. The role of the primary care physician thus becomes even more crucial. Coordination of care with speech and language specialists as well as educators who have experience working with children with deafness is essential. Parents or guardians and other family members may initially be devastated by the diagnosis of a hearing impairment, especially if the deficit is severe to profound. These individuals often have multiple questions about the child's medical prognosis and educational future. The possibility of further speech and language development may also be a foremost concern in their minds. In addition to providing the patient with comprehensive care, all the questions and concerns of the parent or guardian must be addressed and anticipated.

Future Audiologic Evaluations

In the newly diagnosed patient with SNHL, audiology testing should be repeated every 3 months in the first year after birth, every 6 months when the child is in preschool, and at least annually after the child has begun school. Continued monitoring is essential to detect any progression of the hearing deficit.

Assistive Devices

Although hearing aids may not restore normal hearing, all children with CHL as well as SNHL benefit from amplification. Several different types of hearing aids are available for children; these devices should be fitted appropriately and adjusted regularly by a specialist. Additionally, it is also recommended that all patients receive bilateral hearing aids to improve auditory localization and training, particularly in the context of different learning situations.

A frequency modulation system is an additional assistive listening device that can be used in a classroom. A speaker (eg, the teacher) uses a microphone to transmit to a receiver worn by the child to improve reception. Closed-caption television, whether signed or subtitled, is another method of auditory training. Teletype telephone systems are available for children who can read.

Cochlear implants may be surgically placed in the cochlea to improve hearing. Implants were first approved by the US Food and Drug Administration for use in children in 1990. The implant consists of an electrode array placed in the cochlea with a receiver-stimulator under the skin and a processor worn over the ear that transmits by radio waves an impulse that produces an electrical discharge within the cochlea. These electrical pulses effectively stimulate the auditory system. The implant can be used in children 12 months or older with severe to profound SNHL. Its use is now considered to be standard of care for patients with SNHL and is being used in infants as young as 6 months. Speech, language, and special education resources should be provided. Most patients with implants show significant improvement in communication skills. Children with cochlear implants are

at increased risk for meningitis; therefore, pneumococcal and routine *H influenzae* type b vaccines are recommended.

Education and Communication

Much controversy exists concerning the optimal method of communication for children with deafness. Oral communication (ie, lip reading) and sign language each has advantages and disadvantages depending on the child's age, type of deafness, and whether the deficit is congenital or acquired. Whether the child already knows a language is also important to consider. The preferred methods seem to vary from region to region; therefore, schools, other institutions, and resource groups often use the most popular communication method in a particular area. Generally, some authors recommend that children with minimal hearing loss may do better with lip reading than those with greater hearing loss, who will most likely benefit more from sign language. Early intervention and education programs can be home-based or in a group setting, but it is recommended that educators be familiar with working with children with hearing impairment.

Whether to mainstream the child with severe hearing loss in a regular classroom with an interpreter or place the child in a school for children with deafness is another controversial issue. Parent(s)/guardian(s) should be encouraged to explore the possibilities of each option and to make a decision based on the individual needs of the child rather than on current trends. The expertise of an educator who is knowledgeable in this field can be helpful when making this decision.

Outside Resources and Referrals

As previously mentioned, it takes a team to properly evaluate a child with hearing loss. The newly diagnosed child should be evaluated by an otolaryngologist with pediatric expertise, an audiologist, a pediatric ophthalmologist, and a medical geneticist. Any refractory error should be managed and followed closely, because the child with severe hearing difficulty is more dependent on vision. A genetics evaluation is important for diagnostic reasons as well as for providing families with information and counseling about the risk of recurrence.

Speech assessment and therapy are an essential part of long-term management, as are special education resources. Support groups and referrals to national organizations for individuals with hearing impairment can be valuable for parents/guardians and families. Resources for financial support should also be explored. Agencies with multidisciplinary teams are particularly important for newborns, infants, and children with other associated disabilities.

Prognosis

The goals of early recognition and treatment of newborns, infants, and children with hearing deficits are to minimize possible long-term sequelae of persistent speech and language problems and maximize cognitive development. An additional goal is to prevent learning disabilities with subsequent educational failure. The earlier the intervention, the more likely children are to succeed and maximize their potential. With appropriate treatment, the child with hearing impairment should be able to lead a normal life.

CASE RESOLUTION

The child has a history that is classically positive for a hearing deficit. She does not turn to loud noises, she has not developed any specific words, and she indicates her needs nonverbally. Although obvious historical risk factors for hearing loss are lacking, behavioral audiography or brainstem auditory evoked response should be performed by an audiologist. The physician's suspicion should be discussed with the family, and a follow-up visit should be arranged to review hearing test results as soon as possible.

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CHAPTER 89

Sore Throat

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CASE STUDY

An 8-year-old girl has had a sore throat and fever for 2 days. She also has pain on swallowing, a headache, and a feeling of general malaise but no stridor, drooling, breathing difficulty, or rash. Other than the current illness, the girl is in good health. Although she has had sore throats in the past, she has never had one this severe. One week previously, her mother and father had sore throat and fever that resolved after 5 days with no medication.

The child has a temperature of 39.0°C (102.2°F). The physical examination is normal except for red tonsils with exudate bilaterally, palatal petechiae, and tender cervical lymphadenopathy.

Questions

1. What are the causes of sore throat in children?
2. What is the appropriate evaluation of the child with sore throat? What laboratory tests are necessary?
3. What is the appropriate management for the child with sore throat?
4. When should otolaryngologic consultation be obtained?

Sore throat, which is among the most common illnesses seen by the primary care physician, is a painful inflammation of the pharynx, tonsils, or surrounding areas. In most cases, children with sore throat have mild symptoms that require little or no treatment. However, sore throat may be the presenting symptom of a severe illness, such as epiglottitis or retropharyngeal abscess. Young children may not able to define their symptoms very well, which makes a careful history from parents or other caregivers and a good physical examination essential for correct diagnosis. Optimal management of sore throat, especially if group A β-hemolytic streptococcus (GABHS; *Streptococcus pyogenes*) is suspected, remains quite controversial.

Epidemiology

In the United States, sore throat accounts for approximately 15 million outpatient physician visits each year, and approximately 5% of all pediatric emergency department visits are for pharyngitis. Sore throat is most common in children between 5 and 15 years of age. It is uncommon in infants younger than 1 year. Like other respiratory infections, sore throat occurs most often in the late fall and winter months. Approximately 11% of all school-age children receive medical care for pharyngitis. Twenty percent to 30% or more of cases of pharyngitis in these children are caused by GABHS. The estimated medical and nonmedical costs for GABHS pharyngitis are $205 per visit or approximately $224 million to $539 million per year, with much of the indirect costs related to parental loss of time from work.

The organisms that cause bacterial and viral pharyngitis are present in saliva and nasal secretions and are almost always transmitted by close contact. Spread between children in school is the common mode of transmission.

Clinical Presentation

The clinical presentation of sore throat is variable and often depends on etiology (Box 89.1; also see Differential Diagnosis). Most children with sore throat present with sudden onset of pain and fever. The height of the fever is variable and is typically higher in younger children. In the older child, especially if the sore throat is associated with a common cold, fever is minimal or absent. The throat or tonsils are red, and the breath may be malodorous. Headache, nausea, vomiting, and abdominal pain may occur, especially if the child is febrile. Appetite may be decreased, and the child may be less active than usual.

In the child with the common cold, rhinorrhea and postnasal discharge are present. A pharyngeal and tonsillar exudate is not typical. Although the cervical lymph nodes may be enlarged, they are usually not very tender. In contrast, the child with streptococcal pharyngitis typically has high fever, pharyngeal and tonsillar exudate, and tender cervical lymph nodes.

Pathophysiology

Various bacteria and viruses produce sore throat symptoms by causing inflammation in the ring of posterior pharyngeal lymphoid tissue that consists of the tonsils, adenoids, and surrounding lymphoid tissue. This ring of tissue, called Waldeyer tonsillar ring, drains the oral and pharyngeal cavity and defends against infection of the mouth and throat. Other host defenses that protect against infection include the sneeze, gag, and cough reflexes; secretory immunoglobulin A; and a rich blood supply.

Viral sore throat may be acquired by inhalation or self-inoculation from the nasal mucosa or conjunctiva. The local respiratory

Box 89.1. Diagnosis of Sore Throat

Viral Etiology

- Pain in throat
- Fever (variable)[a]
- Rhinorrhea (common)
- Cough (common)
- Erythema of pharynx or tonsils
- Follicular, ulcerative, exudative lesions of pharynx or tonsils[a]
- Conjunctivitis
- Non-scarlatiniform rash
- Occipital or posterior cervical adenopathy

Bacterial Etiology

- Pain in throat, usually sudden onset
- Fever
- Marked erythema of pharynx, tonsils, or uvula
- Headache, nausea, vomiting, abdominal pain
- Tonsillar and posterior pharyngeal wall exudate
- Tender, swollen cervical lymphadenopathy
- Scarlatiniform rash
- Absence of rhinorrhea or cough
- Positive rapid antigen test or throat culture result
- Distortion of natural anatomy

[a] Dependent on etiology (see Differential Diagnosis).

epithelium becomes infected with the virus, and inflammation occurs. In some instances, inflammatory mediators may be responsible for the pain of sore throat. Group A β-hemolytic streptococcus and other bacterial organisms directly invade the mucous membranes. Enzymes produced by this organism, streptolysin O and hyaluronidase, aid in the spread of infection.

Differential Diagnosis

Although most children who present with sore throat have common viral or bacterial pharyngitis, other, less common disorders should be considered, such as infectious mononucleosis, acute HIV seroconversion syndrome, epiglottitis, retropharyngeal abscess, and peritonsillar abscess. See Box 89.2 for a list of causes of sore throat.

Viral Infection

Viral infection, the most common cause of sore throat in children, is most often associated with an upper respiratory infection caused by a rhinovirus. Cough and rhinorrhea associated with a sore throat are suggestive of this etiology. Influenza virus infections may present with sudden onset of high fever, headache, cough, sore throat, and myalgia.

Adenovirus often results in exudative pharyngitis, frequently in children younger than 3 years. Pharyngoconjunctival fever, caused by adenovirus 3, is characterized by a high fever (temperature >39.0°C [>102.2°F]) for several days, conjunctivitis, and exudative tonsillitis.

Coxsackievirus and echovirus, both of which are enteroviruses, are the usual cause of herpangina. Vesicles and ulcers are generally apparent on the anterior tonsillar pillars and soft palate. They may also be found on the tonsils, pharynx, or posterior buccal mucosa. The child may have a high fever (temperature >39.0°C [>102.2°F]), be irritable, and refuse to eat or drink; dehydration may result. Coxsackievirus A16, coxsackievirus A6, and enterovirus 71 cause

Box 89.2. Causes of Sore Throat

Viral Infections

- Adenovirus
- Coxsackievirus
- Echovirus (enteroviruses)
- Common cold
- Cytomegalovirus
- Enteroviral infections
- Epstein-Barr virus
- HIV seroconversion syndrome
- Human herpesvirus
- Influenza virus
- Mononucleosis
- Rhinovirus
- Respiratory syncytial virus

Bacterial Infections

- *Arcanobacterium haemolyticum*
- *Chlamydophila pneumoniae*
- *Chlamydia trachomatis*
- *Corynebacterium diphtheriae* (diphtheria)
- *Francisella tularensis* (tularemia)
- *Fusobacterium necrophorum*
- Group A β-hemolytic streptococcus
- Group B, C, and G β-hemolytic streptococci (non-GABHS)
- *Haemophilus influenzae* type B
- *Mycoplasma pneumoniae*
- *Neisseria gonorrhoeae*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Treponema pallidum* (syphilis)

Other Causes

- Abscess (peritonsillar or retropharyngeal)
- Allergic rhinitis with postnasal drip
- Burns
- *Candida albicans*
- Caustic material
- Cigarette smoke (including secondhand smoke)
- Croup
- Kawasaki disease
- Marijuana smoke
- Odontogenic infections
- Trauma
- Tumors
- Vaping

hand-foot-and-mouth disease, which is characterized by ulcerative oral lesions on the tongue and buccal mucosa and, less frequently, on the palate and anterior tonsillar pillars. Vesicular and papulovesicular lesions are evident on the hands and feet and occasionally on other parts of the body, most commonly the knees and buttocks. It usually occurs in children younger than 5 years but can occur in older children as well. A more severe form of hand-foot-and-mouth disease is associated with coxsackievirus A6, a virus new to the United States in 2012. Enterovirus 71 is sometimes associated with severe central nervous system disease. Enteroviral infections typically occur in the late spring, summer, and early fall.

Human herpesvirus may lead to pharyngotonsillitis but can be distinguished from most of the enteroviral infections because human herpesvirus almost always involves the anterior portion of the mouth and lips and is associated with gingivitis (ie, herpetic gingivostomatitis). The lesions often appear as whitish-yellow plaques with an erythematous base and are sometimes ulcerative. This illness is characterized by a high fever (temperature >39.0°C [>102.2°F]) for up to 7 to 10 days and frequent refusal to eat or drink because of the painful lesions. Dehydration may occur.

Epstein-Barr virus (EBV) may cause exudative pharyngotonsillitis alone or as part of the infectious mononucleosis syndrome that includes fever, malaise, lymphadenopathy, palatal petechiae, and hepatosplenomegaly. Fatigue, malaise, eyelid edema, organomegaly, and a maculopapular rash without the other characteristics of a scarlet fever rash help distinguish between infectious mononucleosis and GABHS infection.

Cytomegalovirus may cause an infectious mononucleosis syndrome similar to EBV but is less commonly associated with pharyngitis and splenomegaly.

HIV seroconversion syndrome may present with low-grade fever, myalgia, nonexudative pharyngitis, diffuse adenopathy, anorexia, and weight loss. Generally, onset of symptoms is approximately 1 week after exposure but may not appear until 1 month after exposure.

Bacterial Infection

Group A β-hemolytic streptococcus is the most common cause of bacterial sore throat in children older than 3 years. The pharynx is typically very red and sometimes edematous, and the tonsils are red, enlarged, and covered with exudate. Occasionally, the uvula is quite inflamed as well. The child may also have dysphagia, fever, vomiting, headache, malaise, and abdominal pain. Swollen anterior cervical lymphadenopathy and petechiae on the soft palate and uvula are usually apparent. Additionally, the occurrence of a scarlatiniform rash, strawberry tongue, and Pastia lines (ie, petechiae in the flexor skin creases of joints) is indicative of scarlet fever, which is diagnostic of group A streptococcal infection (see Chapter 139). Sore throat from GABHS typically occurs in the winter and early spring. Rheumatic fever and glomerulonephritis are nonsuppurative complications of group A streptococcal infection.

Peritonsillar abscess or cellulitis and cervical lymphadenitis are suppurative complications of GABHS. Children with peritonsillar abscess often experience trismus and drooling and speak with a "hot potato" voice. The abscess in the affected tonsil causes a bulge in the posterior soft palate and pushes the uvula away from the midline to the unaffected side of the pharynx. On palpation, the abscess may feel fluctuant. Peritonsillar cellulitis typically produces a bulge in the soft palate but does not cause deviation of the uvula.

Parapharyngeal and retropharyngeal abscesses that typically occur in children younger than 6 years are additional life-threatening complications of GABHS. Sore throat is associated with these conditions, but dysphagia is usually more evident when the child swallows. The child with a retropharyngeal or parapharyngeal abscess is toxic-appearing, also reports trismus, has a fever, has dysphonia, refuses to swallow, and drools. Additionally, the child may have meningismus and may be short of breath. A fluctuant mass may be palpated deep to the tonsils. The patient may have pain when the trachea is manipulated in a lateral direction. The neck may be stiff, and the patient may resist passive neck movements. Stridor may be present but usually is an ominous sign of impending airway compromise.

Group B, C, and G β-hemolytic streptococci (non-GABHS) have all been isolated from children with pharyngitis. *Streptococcus pneumoniae* and *Arcanobacterium haemolyticum* infrequently cause pharyngitis in children. The latter organism is associated with a scarlatiniform rash in some patients and is most common in adolescents and young adults. In contrast with scarlet fever, palatal petechiae and strawberry tongue are not present with the pharyngitis caused by this bacterium. Although *Corynebacterium diphtheriae* (diphtheria) rarely causes sore throat in immunized children, this organism should be considered in nonimmunized children or children from developing countries with exudative pharyngotonsillitis and a grayish pseudomembrane that bleeds when removal is attempted.

Chlamydia trachomatis may result in pharyngitis and tonsillitis in adolescents and young adults through sexual transmission. The role of *Chlamydophila pneumoniae* as a cause of sore throat in children remains unclear. *Mycoplasma pneumoniae* does not usually produce sore throat in children unless they have lower respiratory tract disease. *Neisseria gonorrhoeae* may cause sore throat in sexually active adolescents. Its occurrence in prepubertal children is often secondary to sexual abuse. The appearance of the throat is not characteristic, and diagnosis is made by cultures when the degree of suspicion is high. Tularemia is a rare cause of exudative pharyngitis in children but should be suspected if contact with wild animals has occurred.

Fusobacterium necrophorum is a gram-negative anaerobe that may cause an exudative pharyngitis, tender adenopathy, and fever. Untreated, it may progress to Lemierre syndrome or septic thrombosis of the internal jugular vein. Direct extension of the bacterial pharyngitis leads to perivenular inflammation and septic thrombosis of the internal jugular vein. The patient may present with fever, severe lateral neck pain, torticollis, and prominent internal and external jugular veins with erythema and induration. The patient may also present with additional signs and symptoms if septic emboli propagate, including acute neurologic signs (eg, central nervous system

retrograde propagation), and shortness of breath as a result of multilobar pneumonia with or without cavitation (ie, pulmonary propagation). Paradoxical septic emboli may cause other symptoms if a right-to-left cardiac shunt is present.

Other Causes

Candida albicans may be responsible for sore throat in the infant or child who is immunocompromised or taking antibiotics. The child with oral candidiasis usually presents with whitish plaques on the labial or buccal mucosa that do not wipe off easily. When the pharynx and tonsils are involved, some discomfort or dysphagia, but usually not significant pain, may occur.

Epiglottitis (ie, supraglottitis) may present as sore throat. Prior to the *Haemophilus influenzae* type B (Hib) conjugate vaccine, epiglottitis typically affected children 2 to 7 years of age who would present with signs of toxicity, stridor, difficulty swallowing, and drooling. In the relatively well-appearing child with sore throat but no stridor, neither epiglottitis nor retropharyngeal abscess is a likely cause of sore throat. Historically, epiglottitis was almost always caused by Hib. With the widespread use of the Hib conjugate vaccine, however, this organism is now rarely the etiology, the prevalence of epiglottitis is diminished, and epiglottitis is rarely the cause of sore throat in children. Although rare in adolescents, epiglottitis may present with severe sore throat out of proportion to clinical findings. Other signs and symptoms include dysphagia, odynophagia, a muffled voice, and pain on palpation of the anterior neck around the hyoid bone. *Streptococcus pneumoniae*, *Staphylococcus aureus*, and group A, B, and C β-hemolytic streptococci are unusual but reported causative agents of epiglottitis.

The child with croup may have sore throat and stridor but does not usually appear toxic and does not have difficulty swallowing. Affected children are usually between 6 months and 3 years of age (see Chapter 71).

Odontogenic infections may cause localized infection, inflammation, and swelling of the submental and submandibular space. Significant infection of this space may present with Ludwig angina, which is characterized by difficulty with secretions, dyspnea, airway compromise, and elevated position of the tongue and "woody" induration and tenderness of the sublingual space.

Trauma from penetrating objects, burns, or exposure to caustic materials may cause sore throat in children. Household cigarette smoking, marijuana smoking, and vaping may also result in pharyngeal irritation. Additionally, allergic rhinitis with postnasal drip may result in sore throat. Tumor rarely causes sore throat in children but should be considered if a mass is present or pharyngeal inflammation persists. Persistent sore throat may also be a symptom of Kawasaki disease.

Evaluation

History

A thorough history often reveals the etiology of the sore throat (Box 89.3). Questions about duration, fever, headache, vomiting, pain on swallowing, rash, oral lesions, abdominal pain, and history of contact with other family members or classmates with similar symptoms suggest the most common causes of sore throat (eg, infections with viruses and GABHS). A history of rapid onset of fever, toxicity, difficulty swallowing, drooling, and respiratory distress is suggestive of epiglottitis and retropharyngeal abscess. Voice changes are suggestive of peritonsillar abscess or tonsillar hypertrophy associated with infectious mononucleosis (ie, EBV). Immunization history or history of immigration from a developing country is helpful in assessing the risk of diphtheria. Oral sexual activity suggests the possibility of a sexually transmitted infection. A history of allergies, trauma, and environmental smoke may help diagnose other causes of sore throat. Red eye or pinkeye with a rash, persistent fever (>5 days), and sore throat are suggestive of Kawasaki disease. A teenager with at-risk behavior and an influenza-like illness may be presenting with HIV seroconversion syndrome.

Box 89.3. What to Ask

Sore Throat

- How long has the child had a sore throat?
- Does the child have fever, headache, or vomiting?
- How rapid was the onset of fever?
- Does the child have pain on swallowing?
- Are there any voice changes?
- Does the child have a rash or oral lesions?
- Does the child have abdominal pain?
- Does the child have any ill contacts?
- Are the child's immunizations current?
- Is the child having any difficulty breathing?
- Does the child have a history of allergies?
- Has the child suffered any trauma to the throat or neck?
- Has the child been exposed to environmental smoke?
- For the sexually active adolescent or child with a history of sexual abuse with nonresponding sore throat, has there been any oral sexual activity? Any other risk-taking behavior?

Physical Examination

A general physical examination should be performed. It is important to note whether the child appears toxic or if respiratory distress is present. A child in the tripod position or with drooling should be kept in a position of comfort, taking care not to agitate or further distress the child. The child with stridor at rest should be examined in a position of comfort. Further agitation, distress, or attempts at examination of the oropharynx in these patients can precipitate airway obstruction. The skin should be examined for a scarlatiniform, sandpaper-like rash; a vesicular rash involving the hands and feet; or a generalized maculopapular rash. The eyes should be evaluated for conjunctivitis and the nose for rhinorrhea (serous or purulent). The mouth, pharynx, and tonsils should be examined for vesicular lesions, ulcers, and gingivitis. The pharynx should be checked for redness, exudate, vesicles, edema, and foreign bodies. The tonsils and uvula should be examined for these same findings as well as

asymmetry, and the neck should be checked for nuchal rigidity. The lymph nodes should be evaluated for enlargement (adenopathy) and tenderness (adenitis). The abdomen should be examined for hepatosplenomegaly.

Laboratory Tests

Although many signs and symptoms may be suggestive of streptococcal pharyngitis, diagnosis can be confirmed only with laboratory tests. The throat culture is the standard for diagnosis. When done correctly, throat culture has a sensitivity of 90% to 95% in detecting pharyngeal GABHS. Specimens should be obtained from the surfaces of both tonsils and posterior pharynx without touching other parts of the pharynx or mouth. The main disadvantage of throat culture is that the results are not available for a day or more after the specimen is obtained. Nevertheless, throat culture is the most reliable means of confirming streptococcal infection.

Rapid antigen detection tests (RADTs) are available for on-the-spot diagnosis. False-positive results are uncommon (specificity ≥ 95%), but false-negative results for most RADTs occur commonly (sensitivity 80%–90%). Because a negative test may not exclude a streptococcal infection, guidelines recommend that a negative result be confirmed by throat culture. Because RADTs are highly specific, it is not necessary to confirm a positive test result with a throat culture.

Newer RADTs using optical immunoassay (OIA) and chemiluminescent DNA probes boast sensitivities of greater than 99%. A recent Cochrane review, however, demonstrates a pooled sensitivity of RADTs of 85% with a specificity of 95%. A throat culture in the setting of a negative RADT is still beneficial given the sensitivity.

Rapid and sensitive OIA RADTs reduce antibiotic prescription rates by 50% in pediatric emergency care visits related to sore throat. An antistreptolysin-O titer and an anti-deoxyribonuclease-B titer are not useful for the acute diagnosis of GABHS infection because these titers do not increase until 1 to 2 weeks after the onset of pharyngitis and peak at 3 to 4 weeks. However, measurement of these titers may help confirm a prior streptococcal infection if the throat culture is negative, particularly in the child for whom exists a high index of suspicion for acute rheumatic fever or acute poststreptococcal glomerulonephritis. Diagnostic studies are typically not necessary for children younger than 3 years because GABHS pharyngitis is uncommon and the risk of developing acute rheumatic fever and suppurative complications is low. The role of antibiotic prophylaxis for household contact of patients with acute GABHS is not recommended. Symptomatic contact should be evaluated with an RADT or throat culture.

Differentiating between viral and bacterial pharyngitis is often difficult, and rapid streptococcal antigen tests and throat cultures should be reserved for the patient with signs and symptoms common for both illnesses. Some children have clinical findings that are not consistent with bacterial pharyngitis. For example, the afebrile child with a sore throat, runny nose, and cough who has slight pharyngeal erythema almost certainly has viral pharyngitis and does not require further workup. However, the child with a constellation of signs and symptoms suggestive of bacterial pharyngitis, such as sudden onset of sore throat, fever, headache, swollen and erythematous tonsils, tonsillar or posterior pharyngeal wall exudate, uvulitis, tender and enlarged cervical lymphadenopathy, absence of runny nose or cough, or exposure to an individual with streptococcal pharyngitis, may warrant further testing with RADT or throat culture to confirm group A streptococcal pharyngitis because an accurate diagnosis cannot be made on clinical grounds alone. Approximately 20% of all children are asymptomatic carriers of GABHS in the pharynx, especially during winter and spring. If tested, these children will be positive for GABHS even though they may have a viral illness and will be unnecessarily treated with antibiotics. Guidelines for clinical prediction have been evaluated and have suggested different approaches to the need for RADT or throat culture and antibiotic management. The Centor criteria were derived and validated in adult patients and overestimate the likelihood of GABHS pharyngitis in children. A modified McIsaac score is more predictive than the Centor criteria in children but is not sufficiently sensitive or specific enough to rely on alone. In a meta-analysis of signs and symptoms predicting GABHS, presence of a tonsillar exudate, pharyngeal exudate, or exposure to strep infection in the previous 2 weeks (positive likelihood ratios of 3.4, 2.1, and 1.9, respectively) and the absence of tender anterior cervical nodes, tonsillar enlargement, or exudate (negative likelihood ratios of 0.6, 0.63, and 0.74, respectively), were most predictive. Guidelines that recommend identifying patients who are likely to have group A streptococcal pharyngitis based on clinical or epidemiologic findings and providing antibiotics for only those confirmed by RADT or throat culture decrease the unnecessary overuse of antibiotics.

Viral throat cultures and acute and convalescent titers to determine viral pharyngitis are rarely indicated unless systemic infection occurs (eg, herpes encephalitis). Epstein-Barr virus infection can be determined by specific serologic antibody assays, but nonspecific tests for heterophile antibody (eg, mononucleosis spot [ie, monospot] test) are most available and are usually the tests of choice for diagnosing infectious mononucleosis. However, it may be negative in children younger than 4 years or early in the course of the infection. Only 75% of infected children between 2 and 4 years of age and less than 30% of children younger than 2 years are identified by this test. The monospot test, a rapid slide test for heterophil antibodies, may remain positive for months after the infection and incorrectly may suggest the diagnosis of infectious mononucleosis in the child who no longer has this disorder. A complete blood cell count with more than 50% to 60% lymphocytes or more than 10% atypical lymphocytes is suggestive of mononucleosis. When these tests are inconclusive, the specific serologic antibody tests for EBV infection are helpful in establishing the diagnosis. Cytomegalovirus-specific antibody tests should be considered in the patient with a mononucleosis syndrome and negative laboratory test results for EBV. Culture or fluorescent antibody evaluation of the pseudomembrane may be used to diagnose diphtheria. Culture or presence of serum agglutinins confirms tularemia. Thayer-Martin culture plates should be used to diagnose suspected gonorrheal sore throat. HIV antibody tests are of little use in the evaluation of acute seroconversion syndrome

because antibody titers take 4 to 6 weeks to become detectable. If acute seroconversion is suspected, quantitative RNA polymerase chain reaction should be ordered for HIV.

Imaging Studies

If epiglottitis or retropharyngeal abscess is suspected but not clinically apparent, a lateral neck radiograph may be obtained. Radiography should be performed with a physician in attendance who is capable of performing endotracheal intubation in case the child has respiratory failure (see Chapter 71). Computed tomography of the neck is indicated in the stable patient with suspected deep parapharyngeal or retropharyngeal infection. Emergency bedside ultrasonography is an effective and sensitive tool for differentiating between peritonsillar cellulitis and a peritonsillar abscess.

Management

Management of sore throat in children is based on the etiology of the condition. The early recognition of potentially serious conditions based on history and physical examination is essential to providing optimal care. Otolaryngologic consultation should be obtained for the child with peritonsillar abscess, retropharyngeal abscess, parapharyngeal abscess, submental abscess, epiglottitis, significant pharyngeal trauma, or pharyngeal tumor. Recurrent tonsillitis, especially in the child who misses school, may be a reason for referral to an otolaryngologist.

Outpatient Treatment

For most children with sore throat, the physician must differentiate between viral and streptococcal pharyngitis. Viral sore throat can be managed symptomatically. Treatment with analgesics, such as acetaminophen or ibuprofen to relieve pain, and to promote hydration are the mainstays of therapy for the young child with viral or bacterial sore throat. Gargling with warm water and sucking on hard candy may provide additional symptomatic relief for the older child. The use of steroids for reducing pain for pharyngitis is controversial. One systematic review demonstrated a relatively small reduction in time to significant pain relief of 4.5 hours and a negligible reduction in pain in 24 hours when a single dose of dexamethasone (0.6 mg/kg, maximum 10 mg) is given. However, an additional study in adult patients found a significant reduction in pain at 48 hours after treatment. The decision to administer steroids should be individualized to the patient.

The pain from lesions of herpetic stomatitis often responds to acetaminophen or ibuprofen. Anesthetics, such as lidocaine, may also decrease the pain. A convenient means of delivering lidocaine is in a mixture (1 part each) of lidocaine, diphenhydramine (eg, Benadryl), and a liquid antacid. This mixture, called "magic mouthwash," may be used in the older child. However, little evidence exists supporting a benefit. If used, it may be inserted into each side of the mouth, gargled, or placed on a gloved finger or cotton swab and applied directly on the oral lesions of the tongue and labial and buccal mucosa. It is best used approximately 30 minutes before feeding or drinking, especially in the child who refuses to drink. Lidocaine should be used cautiously because it can suppress the gag reflex. The dose of lidocaine should never exceed 3 mg/kg. Excess lidocaine may result in seizures or arrhythmias. Magic mouthwash can also be prepared without lidocaine, especially for the younger child. The parent or guardian should be given instruction on how to monitor fluid intake and the signs of dehydration.

In the child without clear-cut evidence of streptococcal pharyngitis, a positive rapid streptococcal antigen test helps direct antibiotic treatment. A negative test in the presence of positive symptoms should be accompanied by a throat culture. The OIA rapid test may preclude the need for culture confirmation, however. The patient can await the results of culture before beginning antibiotic therapy. Antibiotics without confirmation from rapid streptococcal tests or cultures are indicated in the child who appears toxic, who has scarlet fever or peritonsillar cellulitis/abscess, or who has a history of rheumatic fever. Most evidence suggests that early treatment results in more rapid clinical improvement, although this is controversial. Rheumatic fever can be prevented if treatment is started within 9 days of sore throat symptom development. Glomerulonephritis likely is not affected by antibiotic therapy.

Evidence suggests that the child with streptococcal pharyngitis should be treated with antibiotics to relieve symptoms, shorten the course of the illness, and prevent disease dissemination, suppurative complications, and rheumatic fever. Penicillin is the antibiotic of choice. It may be administered orally as penicillin V (ie, phenoxymethyl penicillin) in a dose of 250 mg 2 to 3 times a day for 10 days for children (<27 kg [<60 lb]) and 500 mg 2 to 3 times a day for older children, adolescents, and adults. Most patients will feel better after 2 to 3 days, but it is important to stress to the parent(s)/guardian(s) that the children must complete the full 10-day course. Amoxicillin, given once a day orally (50 mg/kg; maximum, 1,000 mg) for 10 days is as effective as penicillin V given 2 to 3 times a day for 10 days, making compliance more likely. Additionally, amoxicillin is more acceptable to young children because the oral suspension is better tasting. No significant difference in treatment success exists between antibiotics. (See Table 89.1 for dosages.)

If the risk of noncompliance is high or if the risk of complication is great (eg, child with a history of rheumatic fever), penicillin should be administered intramuscularly. Intramuscular penicillin has 2 disadvantages: pain associated with the injection and increased incidence of a potentially more severe allergic reaction. The dose of benzathine penicillin for the child weighing less than 27 kg (<60 lb) is 600,000 U. The dose for larger children and adults is 1.2 million U. Bicillin C-R, which contains 900,000 U of benzathine penicillin and 300,000 U of procaine penicillin, is a satisfactory alternative form of delivering penicillin intramuscularly in children and may be preferable because it causes less pain and less severe local reaction. This preparation has not been determined to be effective in heavier patients (ie, adolescents and adults); therefore, the benzathine preparation noted previously is recommended for this group. The injection of benzathine penicillin is less painful if it is given after it reaches room temperature (Table 89.1). A first-generation oral cephalosporin, such as cephalexin, is recommended for most children with

Table 89.1. Antibiotics Used in the Management of Sore Throat in Children

Cause of Sore Throat	*Drug*	*Dosage*
Streptococcal pharyngitis	Penicillin V	250 mg 2–3 times per day for children (<27 kg [<60 lb]) and 500 mg 2–3 times per day for adolescents orally for 10 days
	Amoxicillin	50 mg/kg once daily orally for 10 days (maximum 1,000 mg)
	Cephalexin	25–50 mg/kg per day every 12 hours orally for 10 days (maximum 500 mg every 12 hours)
	Clindamycin	30 mg/kg per day in 3 divided doses (maximum 900 mg per day) orally for 10 days (for chronic streptococcal carriers or suspected *Fusobacterium necrophorum*)
	Azithromycin	12 mg/kg once daily orally for 5 days (maximum 500 mg)
	Clarithromycin	15 mg/kg per day every 12 hours orally for 10 days
	Benzathine penicillin	600,000 U (<27 kg [<60 lb]); 1.2 million U (≥27 kg [≥60 lb]) as single intramuscular injection
	Bicillin C-R	900,000 U benzathine penicillin and 300,000 U procaine penicillin for children as single intramuscular injection
	Rifampin	10 mg/kg per dose orally every 12 hours for 4 days (given last 4 days of treatment with penicillin V or benzathine penicillin for chronic streptococcal carriers)
Gonococcal pharyngitis	Ceftriaxone plus Azithromycin or Erythromycin or (if ≥ 9 years of age) Doxycycline	125 mg intramuscularly in a single dose if <45 kg (<99 lb), 250 mg intramuscularly in a single dose if ≥45 kg (≥99 lb) 20 mg/kg (maximum 1 g) orally in a single dose 50 mg/kg per day (maximum 2 g per day) orally every 6 hours for 14 days 100 mg orally 2 times per day for 7 days

penicillin allergy but should not be used in the child with an immediate or type 1 hypersensitivity to penicillin. Clindamycin may also be used for the patient with penicillin allergy; however, the liquid preparation is not palatable and compliance may be poor. Azalides and macrolides, such as azithromycin or clarithromycin, may be substituted in the child with penicillin allergy. These agents are preferred to erythromycin because they are associated with fewer gastrointestinal side effects. Azithromycin has the added advantage of once daily dosing and a shortened course of therapy of only 5 days. Additionally, shorter-duration alternatives to penicillin are superior in time to symptom improvement as well as duration of fever. Macrolide resistance, however, is 5% to 8% in most areas of the United States. Tetracyclines; sulfonamides, including trimethoprim-sulfamethoxazole; and fluoroquinolones are not recommended for the management of streptococcal pharyngitis.

If symptoms persist and the child has a persistently positive throat culture after completing a course of therapy, the child may be re-treated with the same antibiotic, given another oral antibiotic (as noted previously and in Table 89.1), or given an intramuscular dose of penicillin, especially if compliance is in question.

As noted previously, approximately 20% of children are asymptomatic carriers of group A streptococci. Typically, these children do well, and eradication of the bacteria is not necessary. Cultures after treatment are generally not recommended, except for the child with recurring or persistent symptoms or with a previous history of rheumatic fever. In selected cases of children whose throat cultures remain positive, eradication of the pharyngeal carriage should be strongly considered. These indications are as follows: an outbreak of acute rheumatic fever or poststreptococcal glomerulonephritis, an outbreak of group A streptococcal pharyngitis in a closed or semi-closed community, a family history of rheumatic fever, or repeated episodes of documented symptomatic group A streptococcal pharyngitis within a family over several weeks despite appropriate therapy. If cultures remain positive, these children may be treated with benzathine penicillin and oral rifampin for 4 days in an attempt to eradicate the organism (Table 89.1). Clindamycin is reportedly more effective in eradication of the organism from symptom-free carriers (Table 89.1).

Mycoplasma pneumoniae pharyngitis usually is associated with a generalized infection. Because it is often a self-limited illness, antibiotic therapy is unnecessary unless symptoms persist. Treatment with any of the macrolide antibiotics may be helpful. However, clarithromycin and azithromycin have fewer side effects and are likely to produce better compliance. Macrolides are also the drugs of choice for children with *A haemolyticum* pharyngitis.

Diphtheria, which occurs almost exclusively in developing countries, is a life-threatening infection that requires prompt diagnosis

and treatment. Penicillin G or erythromycin must be given to kill *C diphtheriae*; additionally, equine antitoxin must be administered to neutralize the exotoxin. Tularemia pharyngitis is unusual, but if suspected, it is treated with gentamicin.

For gonococcal pharyngitis caused by *N gonorrhoeae*, intramuscular ceftriaxone is the drug of choice (Table 89.1). Additional antibiotic coverage for associated *C trachomatis* infection should be administered. Oral azithromycin or doxycycline should also be given to children 9 years or older (Table 89.1). Azithromycin or erythromycin may be used for the younger child. The child should be examined and cultured for sexually transmitted infections in other sites and should undergo a serologic testing for syphilis at the first visit as well as a repeat test 6 to 8 weeks later. The child should also be evaluated for concurrent hepatitis B and HIV infection. Sexual abuse should be considered in all cases of gonococcal pharyngitis, particularly in the prepubertal child (see Chapters 60 and 145).

Children with croup usually respond to steroids. Oral nystatin can be used in the child with oral candidiasis. The adolescent with uncomplicated peritonsillar abscess may be treated on an outpatient basis in selected cases with needle aspiration and oral antibiotics.

Inpatient Treatment

The child with sore throat should be admitted to the hospital in the setting of airway obstruction or a need for intravenous (IV) hydration or antibiotics. The child with retropharyngeal abscess and epiglottitis requires IV antibiotics and should be managed in consultation with an otolaryngologist. The preadolescent child or adolescent with complicated peritonsillar abscess also requires IV antibiotics. Surgical intervention is indicated if the abscess is fluctuant, the child is toxic or has severe trismus or airway compromise, or no resolution occurs within 24 hours. Needle aspiration may be acceptable in selected cases but this is associated with an increased rate of treatment failure. Intravenous hydration is occasionally needed for patients with severe herpetic stomatitis who will not drink because of pain and who become dehydrated.

The patient with Lemierre syndrome should be admitted and started on IV antibiotics covering a polymicrobial infection, including anaerobic organisms. If *F necrophorum* pharyngitis is suspected, antibiotics covering anaerobes are indicated.

Suspected deep space infection of the pharynx other than uncomplicated peritonsillar abscess requires inpatient admission and treatment. Retropharyngeal and parapharyngeal abscesses usually require incision and drainage during or after antibiotic initiation. Ludwig angina requires IV antibiotics for an uncomplicated cellulitis or an incision and drainage procedure in the operating room. Meticulous monitoring of the patient's airway is required if it is not secured preoperatively.

The role of tonsillectomy or adenotonsillectomy for the child with recurrent sore throat remains controversial. However, the American Academy of Otolaryngology-Head and Neck Surgery convened a panel of clinicians from various disciplines to develop evidence-based guidelines to identify children who are most likely to benefit from tonsillectomy. These guidelines, containing content based on previous work done by Paradise et al about children with recurrent sore throat, have been recently published. Most children with sore throat improve on their own, and recommendations are therefore for watchful waiting in the setting of fewer than 7 documented sore throat episodes in the past year, fewer than 5 per year over the past 2 years, and fewer than 3 per year over the past 3 years. Parental or guardian report does not qualify as documentation. If the number of documented sore throats meets or exceeds these numbers and associated findings exist (eg, temperature >38.3°C [>101°F], cervical lymphadenopathy, tonsillar exudate, positive test for GABHS), the physician may recommend tonsillectomy. Consultation with an otolaryngologist and a period of watchful waiting should be considered. If a child with recurrent sore throat does not meet these criteria, the child should be assessed for other factors that may favor tonsillectomy over observation, including, but not limited to, multiple antibiotic allergy or intolerance, PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and adenitis), or a history of peritonsillar abscess. Although these guidelines are evidence-based and the recommendations are better defined than before, each case should be individualized. As with all clinical decisions, a role exists for shared decision-making with the child's caregiver and primary care physician about the need for tonsillectomy.

Education

Patients and families should receive general education about sore throat. Medication for pain with drugs such as acetaminophen or ibuprofen is useful, especially if the child is having difficulty swallowing. Gargling with warm salt water or sucking on hard candy may soothe the pain of sore throat. For the child with herpetic gingivostomatitis, avoidance of acidic or spicy food products may prevent pain during eating. The child with bacterial pharyngitis may return to school after 24 hours of antibiotic therapy and the disappearance of fever. Children are likely noninfectious 12 hours after a single dose of amoxicillin. It should be recommended that symptomatic family members see a physician. The parent(s)/guardian(s) should call or return to the physician if the child has respiratory or swallowing difficulties, drooling, severe pain, or fever (temperature >38.3°C [>101°F]) for more than 48 hours after the initiation of appropriate antibiotics.

Prognosis

The prognosis for the child with viral sore throat is excellent because of its self-limited nature. The outlook for the child with streptococcal sore throat is also excellent. If the infection is not diagnosed and managed appropriately, however, suppurative (eg, peritonsillar abscess) and nonsuppurative complications (eg, rheumatic fever, acute glomerulonephritis) may occur. With early diagnosis and prompt treatment, the prognosis for unusual, life-threatening causes of sore throat is also very good. The cross-immunogenicity of GABHS presents a unique and challenging case for vaccine development.

CASE RESOLUTION

The child has palatal petechiae and tonsillar exudate, which are signs and symptoms consistent with streptococcal pharyngitis. A streptococcal RADT is performed and is positive. The child is treated with oral penicillin. Neither of her parents has sore throat symptoms.

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CHAPTER 90

Nosebleeds

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CASE STUDY

A 3-year-old boy is brought to the office on a winter day. He has had 4 nosebleeds in the past week as well as a cold with rhinorrhea and cough, which began the day before the first nosebleed. The nosebleeds occur at night or during sleep and stop spontaneously or with gentle pressure. Other than the cold and nosebleeds, the boy is in good health. He is active, with bruises over both tibias but none elsewhere. The many cuts and scrapes he has had in the past resulted in minimal bleeding. His family has no history of a bleeding disorder or easy bruising.

The child's physical examination is entirely normal except for a small amount of blood in the left anterior naris.

Questions

1. What are the common causes of nosebleeds in children?
2. What systemic diseases are associated with nosebleeds?
3. How should nosebleeds be evaluated in children?
4. How should minor and severe nosebleeds be managed in children?

Nosebleed, or epistaxis, occurs commonly in children, especially in those between 2 and 10 years of age. In most cases, nosebleeds are secondary to local trauma and can be managed by primary care physicians. In rare instances, however, a nosebleed may be difficult to control or may be a manifestation of a serious systemic illness. Referral to an otolaryngologist or a hematologist/oncologist is usually not required except in these situations, and hospitalization is generally unnecessary. Parents and children often are frightened by nosebleeds and frequently overestimate the amount of blood lost. Providing reassurance and a basic understanding of the most common causes are important in allaying anxiety.

Epidemiology

Thirty percent of children experience 1 nosebleed by 5 years of age. In children between the ages of 6 and 10 years, the frequency increases to 56%. Nosebleeds are rare in infancy, with an estimated 1 nosebleed per 10,000 patients younger than 2 years. Nosebleeds are infrequent after puberty. They occur much more frequently in the late fall and winter months, when upper respiratory infections (URIs) are common, environmental humidity is relatively low, and the use of heating systems may result in dryness. Nosebleeds are also more common in children who live in dry climates, especially in the presence of a concomitant URI or chronic allergic rhinitis.

Clinical Presentation

Most children with nosebleeds have a history of bleeding at home and have minimal or no bleeding at the time of presentation (Box 90.1). However, children with underlying clotting disorders (eg, hemophilia) may have recurrent nosebleeds and a history of prolonged bleeding, easy bruising, or multiple bruises in uncommon locations such as the gingivae or joints. Less commonly, nosebleeds are among the first manifestations of an undiagnosed malignancy or other systemic illness. In unusual situations, children with gastrointestinal or respiratory tract bleeding may present with blood exiting through the nose. Alternatively, some children with nosebleeds may present with hematemesis, hemoptysis, melena, or anemia. In these cases, a nasal source should be considered.

Box 90.1. Diagnosis of Epistaxis

- Blood in anterior nares, nasopharynx, or mouth
- History of any of the following:
  - — Frequent digital manipulation (ie, nose picking)
  - — Upper respiratory infection (recent)
  - — Allergic rhinitis
  - — Dry climate
  - — Foreign body in nose
  - — Trauma to nose
  - — Prolonged or difficult-to-stop bleeding, or easy bruising
- Physical examination consistent with any of the following:
  - — Rhinorrhea
  - — Dry, cracked nasal mucosa
  - — Foreign body in nose
  - — Trauma to nose
  - — Multiple bruises

Nosebleeds are generally categorized by anatomic location as anterior or posterior. Anterior epistaxis is most common, comprising 90% of pediatric nosebleeds, and is almost always self-limited. With

anterior nosebleeds, vessels from the anterior portion of the nose rupture, resulting in readily visible blood loss through the nares. With posterior nosebleeds, most of the blood runs into the nasopharynx and mouth, although some blood may exit through the nose as well. Posterior nosebleeds, though uncommon in children, tend to be heavier and more difficult to control, and children have a propensity to become hemodynamically unstable.

Pathophysiology

More than 90% of nosebleeds in children are anterior and easily controlled. Anterior bleeding originates approximately 0.5 cm from the tip of the nose, known as the Kiesselbach area. This area is a confluence of small vessels supplied by the anterior and posterior ethmoidalarteries, the sphenopalatine artery, and the septal branches of the superior labial artery (Figure 90.1). The mucosa covering the Kiesselbach area is thin and friable, providing little structural support to the small vessels supplying the nasal mucous membrane.

The congestion of vessels located in the Kiesselbach area as the result of URIs or drying of the mucosa secondary to low environmental humidity makes this area susceptible to bleeding. Viral respiratory infections, such as infectious mononucleosis and influenza, may predispose children to nosebleeds because of the local inflammatory effect of such infections. Nosebleeds in children with these infections are more common in areas of low environmental humidity. Even in the absence of URI-like symptoms, however, children may experience nosebleeds in such environments, especially in the winter, when inhaling dry, hot air from heating systems causes desiccation of the nasal mucosa (ie, rhinitis sicca). Nosebleeds also occur more commonly in children who have nasal colonization with *Staphylococcus aureus*. It is postulated that *S aureus* replaces existing flora and results in inflammation and new vessel formation.

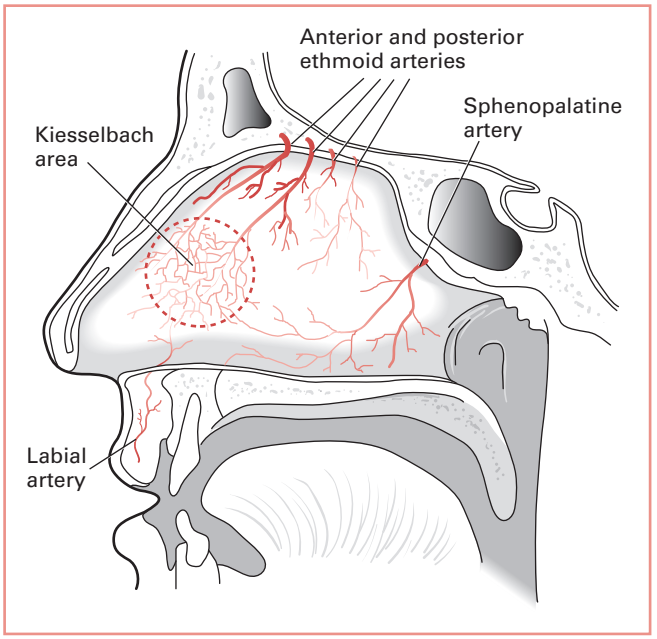

Figure 90.1. Vascular supply of the nasal septum. Note the confluence of vessels that forms the Kiesselbach plexus.

Posterior nosebleeds are unusual in children and are most commonly associated with trauma. If bleeding is vigorous or poorly controlled with anterior nasal packing or involves both nares, a posterior source is likely to be responsible. Posterior nosebleeds generally arise from the turbinate or nasal wall. Significant bleeding, usually from a branch of the sphenopalatine artery, may occur. Because of the posterior location, children often present with symptoms other than frank epistaxis (eg, hematemesis, hemoptysis, melena, anemia).

Differential Diagnosis

Trauma from nose picking and inflammation of the nasal mucosa from a URI are by far the most common causes of nosebleed in children. Repetitive, habitual nose picking (ie, epistaxis digitorum) results in the formation of friable granulation tissue that bleeds when congested blood vessels are traumatized. As the nasal mucosa dries, crust formation and cracking may occur. Bleeding may occur spontaneously or from nose rubbing, but more often it results from forceful nose blowing and sneezing, which increase venous pressure in the more vascularized nasal septum.

Foreign bodies may cause direct trauma or pressure necrosis to the vessels of the nasal mucosa. Toddler-age children may place small toys, beads, pebbles, or food items into the nares. Button batteries are particularly troublesome and should be removed immediately to avoid septal perforation. Children with unilateral epistaxis with purulent or foul-smelling nasal drainage should be evaluated for a foreign body. External trauma secondary to falls or blunt force can cause tears to the nasal mucosa or nasal fractures. If bleeding from mucosal vessels occurs but the mucosa remains intact, a septal hematoma may occur. Thus, it is important to carefully examine the nasal septum. Abscess formation or septal perforation may occur if the septal hematoma is not drained. Non-accidental trauma, specifically asphyxiation, should be considered in any child younger than 2 years with a nosebleed.

Allergic rhinitis with inflammation and subsequent drying also may result in nosebleeds. Airborne environmental pollutants have been associated with increased inflammation of the nasal mucosa. Children with allergic rhinitis who take decongestants or use topical nasal decongestants or topical nasal steroid sprays may have an increased likelihood of experiencing nosebleeds. In addition, the dispenser tip of these sprays may traumatize the already dry and friable mucosa, causing the nose to bleed.

Although nosebleeds are usually benign conditions, they may be among the first signs of serious illness. Persistent or recurrent nosebleeds with no obvious cause should raise the suspicion of bleeding disorders (see Chapter 99). Thrombocytopenia is the most common coagulation defect that results in nosebleeds. Idiopathic thrombocytopenic purpura is the thrombocytopenic disorder most frequently associated with nosebleeds. Leukemia, aplastic anemia, and HIV infection also should be considered and ruled out in children with nosebleeds and thrombocytopenia. Platelet aggregation disorders also may be a cause of recurrent nosebleeds.

The most commonly inherited bleeding disorder associated with nosebleeds is von Willebrand disease, an autosomal-dominant bleeding disorder characterized by varying degrees of factor VIII deficiency and platelet dysfunction (ie, decreased platelet adhesiveness). Hemophilia (factor VIII, IX, or XI deficiency), factor VII deficiency, Glanzmann thrombasthenia, and Bernard-Soulier syndrome are other inherited bleeding disorders that may result in nosebleeds. Hepatic disease, severe vitamin K deficiency, or malabsorption syndrome are associated with acquired coagulopathy, of which nosebleed may be a presenting sign. Administration of valproic acid has been associated with acquired von Willebrand disease and nosebleeds.

Nosebleeds may be a manifestation of hereditary or acquired blood vessel disorders. Hereditary hemorrhagic telangiectasia (ie, Osler-Weber-Rendu disease) is an inherited autosomal-dominant disease with multiple mucosal telangiectasias, especially in the nose. Because telangiectasias are deficient in muscular and connective tissue, they may rupture spontaneously and bleed profusely. An association between migraine headaches and recurrent nosebleeds has also been reported.

Neoplasms, particularly malignancies, are uncommon causes of nosebleeds in children. Although nasal polyps generally are benign, they usually occur in association with cystic fibrosis or allergies. Capillary, cavernous, and mixed hemangiomas may occur in the nose and be a source of bleeding. Juvenile nasopharyngeal angiofibroma occurs almost exclusively in adolescent males who present with nasal obstruction and bleeding. Rhabdomyosarcoma, lymphoma, and squamous cell carcinoma of the nose, sinuses, or nasopharynx are rare causes of nosebleeds in the pediatric population.

Drugs such as aspirin and nonsteroidal anti-inflammatory drugs, which interfere with platelet function, and warfarin and heparin, which inhibit clotting factors, increase the risk for nasal hemorrhage with minor trauma, infection, or inflammation. Unintentional ingestion of these medications should be suspected if they are accessible to the child. Snorting cocaine or heroin may cause nasal septal perforation and nosebleeds. Some complementary and alternative therapies, such as *Ginkgo biloba*, may also be associated with abnormal bleeding.

Hypertension is rarely associated with nosebleeds in children. Wegener granulomatosis and lethal midline granuloma are rare idiopathic inflammatory diseases in children that result in nasal tissue destruction and bleeding. Nosebleeds during menstruation, that is, *vicarious menstruation*, may be secondary to hormonal changes that result in vascular congestion of the nasal mucosa.

Evaluation

History

A thorough history often reveals the etiology of the nosebleed (Box 90.2). Information concerning the side of the nose from which the bleeding occurred, amount of bleeding, measures used to stop the bleeding, and time required to stop the bleeding may be helpful to quickly assess the severity of the nosebleed.

Box 90.2. What to Ask

Nosebleeds

- Does the child pick his or her nose?
- Has the child suffered any trauma recently?
- Is there suspicion of non-accidental trauma?
- Has the child recently had an upper respiratory infection?
- Has the child recently had any systemic viral or bacterial illness?
- Does the child have any allergies?
- Is the child exposed to dry conditions (eg, dry climate, dry heat, dehumidified air)?
- Has the child put or tried to put foreign objects in his or her nose?
- Is there a history of easy bruising or prolonged, difficult-to-stop bleeding in the child or family?
- Does the child or anyone in the family use any aspirin, aspirin-containing medications, nonsteroidal anti-inflammatory drugs, or warfarin?
- Does the child or any family member use cocaine, heroin, inhalants, or any other drugs of abuse?
- Does the child or any family member use complementary and alternative therapies, such as *Ginkgo biloba*?
- Which side of the nose was bleeding? Was it bilateral?
- How extensive was the bleeding?
- Did the child spit out or swallow blood? Was there blood in the mouth?
- What measures were used to stop the bleeding? How long did it take to stop the bleeding?
- Was this the first nosebleed? If nosebleeds are recurrent, how often do they occur and how long do they last?

Physical Examination

A general physical examination should be performed. In children with significant blood loss, particular attention should be directed toward the mental status and vital signs to determine hemodynamic stability. If vital signs are normal, these children should also be evaluated for orthostatic changes. If blood pressure is elevated, it should be reassessed at a time when the anxiety related to the nosebleed has dissipated.

In addition, the skin and mucous membranes should be checked carefully for petechiae, purpura, and ecchymoses, as well as pallor. The conjunctiva may reveal icterus, a sign of liver disease presenting as a coagulopathy. The abdomen should be examined for hepatosplenomegaly and the child should be evaluated for lymphadenopathy, which is suggestive of leukemia. Telangiectasia in the oropharynx or mucous membranes is associated with hereditary hemorrhagic telangiectasia. The oropharynx and nasopharynx should be examined for masses, foreign body, and blood dripping downward from a posterior bleed. Next, the nose should be inspected for the site of bleeding, with particular attention paid to the Kiesselbach area in the anterior septum. In children younger than 2 years with nosebleeds, suspicion of non-accidental trauma should be considered, especially if nosebleeds are recurrent, the event is not witnessed, or the story given by the caregiver changes. In such cases, the patient should be evaluated for burns and other marks that may be indicative of non-accidental trauma.

Diagnostic Studies

Laboratory tests are rarely indicated in most children with nosebleeds. They might be considered for those patients in whom bleeding lasted longer than 30 minutes, patients younger than 2 years, or patients who have experienced more than 2 to 3 episodes of epistaxis each week for several weeks. Hematocrit and hemoglobin tests should be performed if the nosebleeds are severe or recur frequently. For children with signs or symptoms of hypovolemia (ie, increased pulse; cool, clammy skin; increased capillary refill; decreased blood pressure) or a marked drop in hematocrit, blood should be tested for type and crossmatch. If the history or physical examination are suggestive of coagulopathy, a complete blood cell count with platelet count and examination of peripheral smear, prothrombin time, and partial thromboplastin time should be obtained. If these laboratory tests are negative, screening for von Willebrand disease should be considered if the other laboratory tests are negative.

Radiography and other imaging studies are rarely necessary in children with nosebleeds. However, if a mass is visualized, further imaging may be necessary to evaluate it. The most commonly used modalities include magnetic resonance imaging and contrast-enhanced computed tomography. Rarely, pseudoaneurysm of the internal carotid artery has been associated with epistaxis; in these cases, angiography may be required for further evaluation.

Management

Children who present to primary care physicians with a history of 1 or more nosebleeds that have resolved spontaneously or with application of pressure to the nasal alae need no further treatment in the office or emergency department setting, provided that the history and physical examination are consistent with a benign cause. These children or their parents should be instructed to apply a lubricant (eg, petroleum jelly) or an antibiotic ointment, inside the septal portion of the involved naris twice a day for 3 to 5 days with a cotton-tipped swab or little finger. Often the child's little finger is used because it is nonthreatening and it "knows where to go." Further nose picking should be discouraged, and fingernails should be trimmed to minimize trauma. In addition, a bedside humidifier helps moisturize the air, especially in dry climates or during the winter when forced hot-air heat is used. Children whose nares moisten from rhinorrhea and then dry and crack also benefit from humidified air. Buffered saline nasal spray may also be helpful in humidifying the nose. Children who are prone to recurrent nosebleeds and in whom serious causes have been ruled out may benefit from regular use of some of the aforementioned measures when they have URIs or allergic manifestations or are in a dry season or environment. Patients with suspected allergic causes may benefit from the use of an oral antihistamine or topical corticosteroids. In addition, for children with *S aureus* nasal colonization, eradication with a course of mupirocin nasal ointment should be considered.

Children or parents should be given advice about how to care for nosebleeds at home. These instructions can also be given to parents who seek advice over the telephone about how to stop children's nosebleeds. Health professionals should reassure parents and children that most nosebleeds are easily controlled. Children should sit upright and lean forward slightly while direct pressure is applied to the nose. External compression of the nasal alae between the thumb and forefinger for 5 to 10 minutes typically is sufficient. Most nosebleeds originate at the anterior and mid-portion of the nose; thus, application of pressure here is more effective in stopping bleeding than application of pressure at the base of the nose.

Children who are actively bleeding through the nose at the time of evaluation by a primary care physician should be positioned sitting upright and leaning forward slightly, and they should be given a basin and facial tissue. Direct pressure should be applied by a provider or reliable parent to the anterior and mid-portion of the nose while following universal precautions. A cotton dental roll may be placed under the upper lip to compress the labial artery in older children in whom concern about displacement and possible aspiration of the cotton is minimal. If the bleeding continues after external compression, children should be instructed to blow their nose to remove as much clot as possible. Fresh blood should be removed with suction. Cotton pledgets moistened with a few drops of a topical vasoconstrictor, such as 0.05% oxymetazoline (Afrin, OcuClear, Drixine), or topical thrombin should be inserted into the involved side of the nose. Pressure should be applied for an additional 10 minutes. Because phenylephrine has been associated with significant morbidity and mortality when topically applied, it should be avoided in the management of pediatric epistaxis.

If the bleeding persists, cauterization of the bleeding site with a 75% silver nitrate stick is indicated. If not already applied, topical anesthesia with 2% to 4% lidocaine should be applied before cauterization. Continued bleeding is slowed by first cauterizing a small ring around the bleeding point to interrupt flow from surrounding vessels and then rolling the tip of the applicator onto the bleeding site for 5 seconds or less. Cauterization is often difficult in children, and consultation with an otolaryngologist is advised. Cauterization should not be performed in children with a bleeding diathesis. In addition, cauterization should only be done unilaterally. Cauterizing both sides of the nasal septum can result in septal ischemia and possible necrosis and ultimately, septal perforation.

If the bleeding continues, an absorbable nasal sponge made of oxidized cellulose (eg, Merocel, Rhinocell, Surgicel) or gelatin (eg, Gelfoam) may be directly applied to the bleeding site to form an artificial clot. This also may be done to avoid cauterization. Hemostatic seals (eg, Floseal, Avitene) may also be used; these agents are composed of collagen or thrombin derivatives and help support platelet aggregation and clot formation when applied to the bleeding site. Alternatively, nasal tampon, which is made of a dehydrated material that expands when it becomes moist, may be inserted to tamponade the area of bleeding. This method is less well tolerated than an absorbable nasal sponge, however. The application of antibiotic ointment, preferably mupirocin or chlorhexidine-neomycin, to the tampon allows for easier insertion and removal and may prevent *S aureus* colonization

and infection. Another option to stop the bleeding is insertion of an inflatable balloon (eg, Rapid Rhino, Epi-Stat, Epi-max, Post-Stop) coated with a platelet aggregator. Continued uncontrolled bleeding requires anterior nasal packing with gauze strips. Antibiotic-impregnated (preferably with mupirocin), 1-inch petrolatum gauze strips may also be used, although these have not been shown to prevent toxic shock syndrome. The nasal packing should remain in place for approximately 2 to 3 days. Prophylactic antibiotics are not routinely recommended because they have not been shown to prevent toxic shock syndrome. In the patient with evidence of an underlying sinus infection, however, it has been shown that antibiotics that provide coverage for staphylococcal organisms (in particular, methicillin-resistant *S aureus*) and sinusitis should be prescribed. For all patients with packing, an otolaryngologist should be consulted, and the otolaryngologist should be present at the time of packing removal. In general, packing should not be done in patients younger than 1 year because of the risk of aspiration.

Posterior nosebleeds, which are more difficult to control than anterior nosebleeds, should be suspected if the measures described previously are ineffective, bleeding is vigorous and the cause cannot be identified, or most of the bleeding is into the nasopharynx and mouth. A posterior nasal pack can be created using rolled gauze or a nasal tampon. Alternatively, a Foley catheter or an Epi-Stat inflatable nasal balloon catheter may be used to control posterior nosebleeds. Posterior packs should never be used without the presence of a concurrent anterior nasal pack. Thus, a double-balloon catheter (eg, Nasostat, Epi-Stat) can be used, obviating the need for 2 separate packing mechanisms. Posterior packing can result in significant discomfort for the patient, and appropriate analgesia should be provided. However, significant pain with balloon inflation should not occur, and overinflation may result in ischemia if the balloon is not slightly deflated. Posterior packing should be left in place for 2 to 3 days, and antibiotics should be initiated to prevent sinusitis. Additionally, posterior packing can result in hypoventilation and hypoxia. Therefore, all patients with posterior packing should be admitted to the hospital and placed on a cardiorespiratory monitor. This also allows for monitoring of potential complications, such as aspiration caused by unintentional dislodgment of the packing material; septal ischemia secondary to packing; and the development of hypotension, bradycardia, or apnea secondary to a pronounced nasal-vagal response.

The need for consultation with an otolaryngologist is dependent on the experience of the individual physician and availability of consultation. Prompt consultation, if available, should be obtained for children with severe nosebleeds who need volume replacement; with nosebleeds that do not stop or that recur after implementation of the aforementioned measures; who may need anterior or posterior nasal packing; and with recurrent, difficult-to-stop nosebleeds. For patients with suspected nasal fracture, surgical consultation should be sought prior to placement of nasal packing. In some cases, obtaining consultation before cauterization with silver nitrate is advisable, particularly in patients with known bleeding disorders. Children with septal hematoma, tumor, polyp, telangiectasia, and intractable bleeding should be referred to an otolaryngologist for further care and possible surgical intervention. Children with a documented or suspected bleeding disorder should be referred to a hematologist. Selective angiographic embolization (most commonly of the internal maxillary artery) by an interventional radiologist or sphenopalatine artery ligation may be indicated for patients with persistent, intractable nosebleeds. Intranasal laser surgery may be indicated in patients with recurrent nosebleeds resulting from abnormal vascular malformations, such as hereditary hemorrhagic telangiectasia.

In children with severe nosebleeds, an intravenous line should be started early, blood should be sent for type and crossmatch and, depending on the amount of blood loss and physical evidence of hypovolemia, fluid replacement therapy should be initiated. In children who are frightened or in whom certain procedures (eg, cauterization of bleeding site, drainage of septal hematoma) are performed, procedural sedation should be strongly considered. Intravenous pain medication should be used in children who need anterior or posterior packing. If procedures that cause undue pain or discomfort are necessary, general anesthesia in an operating room setting may be indicated.

Children with underlying systemic illness that is causative for nosebleeds may benefit from an individualized approach. For example, platelets should be administered to patients with nonimmune thrombocytopenia, and appropriate factor should be administered to patients with hemophilia. Patients with epistaxis who have von Willebrand disease benefit from packing with cellulose soaked in topical thrombin as well as administration of desmopressin. Replacement therapy with Factor VIII or with recombinant human Factor VIIa depends on the type of von Willebrand disease and their response to local treatment. For patients with immune thrombocytopenia, intravenous immunoglobulin or anti-D immune globulin in conjunction with high-dose steroids has been shown to be effective. Cautery should be avoided in patients with hereditary hemorrhagic telangiectasia; fibrin glue has been shown to be effective in controlling bleeding.

Hospitalization is rarely necessary for children with nosebleeds. However, children who are hemodynamically unstable on presentation usually require inpatient treatment. As mentioned previously, children for whom placement of a posterior nasal pack is required should be admitted to the hospital for close airway observation. Hospitalization may be necessary for children with difficult-to-stop bleeds who need an anterior nasal pack or who have a bleeding disorder or underlying chronic illness, such as leukemia, aplastic anemia, or HIV infection.

Prognosis

The prognosis for nosebleeds in children is excellent. Almost all nosebleeds are easily controlled with a minimal amount of home care or medical management. Surgery is rarely indicated. Complications associated with significant nosebleeds include hypovolemia resulting from blood loss, and sinusitis and toxic shock syndrome resulting from *S aureus* associated with anterior or posterior nasal packing. Recurrent idiopathic epistaxis resolves with time and is uncommon in children older than 14 years. Even for rare causes of nosebleeds, the prognosis is very good with prompt diagnosis and treatment.

CASE RESOLUTION

The boy has experienced several nosebleeds of short duration associated with a URI and winter dryness. His history and physical examination are unremarkable for a bleeding disorder or chronic illness. The small amount of blood in his nose is consistent with an anterior nosebleed originating from the Kiesselbach area, with inflammation and drying of the nasal mucosa. Laboratory tests are not indicated. The parents should be instructed to apply petroleum jelly to the septal portion of the left side of the child's nose twice a day for 3 to 5 days and to humidify the child's bedroom. They should also be reassured that their child has a common condition that he will outgrow.

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CHAPTER 91

Strabismus

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CASE STUDY

The mother of an 8-month-old reports that every time her son looks to either side, his eyes seem crossed. Otherwise, he is growing and developing normally. Symmetric pupillary light reflex, bilateral red reflex, and normal extraocular eye movements in all directions are noted on physical examination of the eyes.

Questions

1. What is strabismus?
2. What conditions make an infant's eyes appear crossed? What is the differential diagnosis?
3. What tests are used in the office evaluation of the child with suspected strabismus?
4. Which infants with crossed eyes require referral for further evaluation and treatment?

The term strabismus refers to any abnormality in ocular alignment, whether the eyes go in or out or 1 eye is higher than the other. It is among the most common eye problems observed in infants and children. The pediatrician plays an important role in the early detection and prompt referral of children with suspected ocular alignment abnormalities.

Epidemiology

Strabismus affects approximately 3% of the population, and the condition occurs most commonly in children younger than 6 years. Approximately 50% of all affected children have a positive family history of strabismus, although the exact genetic mode of inheritance is unclear. Up to 75% of otherwise healthy newborns and infants have transient intermittent strabismus during the first 3 months after birth.

Clinical Presentation

Children with ocular misalignment have an asymmetric corneal light reflex test. Eye movement is noted on cover testing. Children with paralytic strabismus may present with torticollis (ie, head tilt) in an effort to avoid double vision (ie, diplopia; Box 91.1).

Pathophysiology

Normal binocular vision is the result of the fusion of images from both eyes working synchronously across the visual field. Six extraocular muscles control all eye movements. *Orthophoria* is proper alignment of the eyes, and strabismus results from an imbalance in muscle movements.

Strabismus

The classification of strabismus is complex. Based on etiology, it may be considered nonparalytic (comitant) or paralytic (noncomitant). Strabismus may also be classified as congenital or acquired, intermittent or constant, and alternating or unilateral. In *nonparalytic strabismus*, the extraocular muscles and the nerves that control them are normal. The degree of deviation is constant or nearly constant in all directions of gaze. Nonparalytic strabismus is the most common type of strabismus occurring in children, and congenital or infantile esotropia is usually of this type. Ocular or visual defects, such as cataracts or high refractive errors, occasionally cause nonparalytic strabismus.

In *paralytic strabismus*, paralysis or paresis of 1 or more of the extraocular muscles produces a muscle imbalance. The deviation is asymmetric, and characteristically the degree of deviation is worse when gazing in the direction of the affected muscle. Paralytic strabismus may be congenital or acquired. Congenital paralytic strabismus may be the result of birth trauma, muscle anomalies, abnormal development of the cranial nerve nuclei, or congenital infections affecting the eyes. Congenital strabismus may occur in association with neurodevelopmental disorders, such as cerebral palsy. Acquired paralytic strabismus resulting from extraocular muscle palsies usually indicates the presence of a serious underlying condition, such as an intracranial tumor, a demyelinating or neurodegenerative disease, myasthenia gravis, progressive myopathy, or central nervous system (CNS) infection. Children may present with double vision or a compensatory head tilt to avoid double vision.

Intermittent (ie, latent) misalignment of the eyes is referred to as a *phoria*. Under normal conditions, the fusional mechanisms of the CNS maintain eye alignment. Eye deviation is appreciated only under certain conditions, such as illness, fatigue, or stress, or in cases in which fusion is interrupted by occluding 1 eye (eg, during cover testing). Some degree of phoria may be found in almost all individuals and typically, it is asymptomatic. Larger degrees of phoria may give rise to troublesome symptoms such as headaches, transient diplopia, or asthenopia (eg, eyestrain).

Box 91.1. Diagnosis of Strabismus

- Head tilt
- Double vision (ie, diplopia)
- Squint
- Asymmetric corneal light reflex
- Eye movement with cover testing

Constant misalignment of the eyes is referred to as *heterotropia* (ie, strabismus). This condition occurs because normal fusional mechanisms are unable to control eye deviation; children are unable to use both eyes together to fixate on an object. In alternating heterotropia, both eyes appear to deviate equally, and vision generally develops normally in each eye because children have no preference for fixation. If strabismus affects only 1 eye, the other eye is always used for fixation, and a danger exists for the development of amblyopia or vision loss in the deviating eye.

Convergent deviation, which is a turning in or crossing of the eyes, is an esodeviation (eg, esotropia, esophoria). *Divergent deviation*, which is a turning out of the eyes, is an exodeviation. The term *hypertropia* refers to conditions involving upward vertical deviations. Esodeviations are the most common type of ocular misalignment, accounting for 50% to 75% of all cases of strabismus. Vertical deviations represent less than 5% of all cases of strabismus.

Amblyopia

Amblyopia is a potential complication if strabismus is not corrected in a timely manner. *Amblyopia* refers to poor vision in 1 eye or, rarely, both eyes despite correction of any refractive errors. A child with no significant refractive error and with visual acuity of 1 eye that is worse than the other has amblyopia. Diagnosis of amblyopia is based on a difference in visual acuity of at least 2 lines (eg, 20/20 in 1 eye and 20/40 in the other), as measured by reading an eye chart. Amblyopia is the leading cause of preventable visual loss in children.

Amblyopia may be classified into 3 major categories: deprivation amblyopia, refractive amblyopia, or strabismic amblyopia. Generally, *deprivation amblyopia* is the result of obstruction of vision caused by a unilateral lesion or developmental defect in 1 of the structures of the eye or its visual pathways. Causes of deprivation amblyopia include congenital cataract, ptosis, corneal opacity, retinal detachment, retinoblastoma, coloboma, optic nerve defect (eg, optic nerve hypoplasia), and orbital tumor. These conditions cause a lack of formation of a retinal image or a blurred retinal image, usually in 1 eye. *Refractive amblyopia* refers to a blurring of the retinal image resulting from large or asymmetric refractive errors. Amblyopia is usually considered a unilateral abnormality, but it may be bilateral in cases of large refractive errors (usually, astigmatism or hyperopia). In *strabismic amblyopia*, the immature or developing brain suppresses images from the deviating eye to prevent diplopia. Strabismic amblyopia is most commonly associated with strabismus that manifests in children younger than 4 years. If the condition that causes amblyopia is not corrected while the brain's visual pathways are still malleable (eg, before approximately 6–7 years of age), children may experience some degree of permanent visual loss.

Differential Diagnosis

The differential diagnosis of strabismus may be divided into 3 categories: transient neonatal strabismus, congenital or infantile strabismus, and acquired strabismus. It is important to differentiate true strabismus from the illusion of deviation created by facial asymmetry or anatomic variations (ie, pseudostrabismus).

Transient Neonatal Strabismus

Eye alignment in normal newborns and infants during the first 2 to 3 months after birth may vary from normal to intermittent esotropia or exotropia. These deviations are believed to result from CNS immaturity and resolve spontaneously in most infants by 4 months of age. If such deviations are constant or persist beyond this age, the child should be referred to an ophthalmologist for further evaluation.

Congenital or Infantile Strabismus

Congenital or infantile strabismus is deviation that occurs within the first 6 months after birth. Because the deviation may not always be present at birth, the term "infantile" may be more accurate. The differential diagnosis of infantile strabismus is presented in Box 91.2. *Pseudoesotropia* is an illusion or apparent deviation; it is not a true deviation. In many infants, the broad, flat nasal bridge and prominent epicanthal folds may obscure a portion of the sclera near the nose and create the appearance of esotropia (Figure 91.1). This illusion resolves as children mature. Symmetric corneal light reflexes or normal cover tests differentiate pseudoesotropia from true esotropia.

Esotropia is among the more common types of childhood strabismus. The constant deviation of infantile esotropia typically is readily apparent because of the large angle of deviation. Affected children usually have good bilateral vision because of the alternation of fixation from 1 eye to the other. *Cross-fixation*, in which children look to the left with the adducted right eye and to the right with the adducted left eye, may be evident because of the large angle of deviation. Rarely, esotropia may be caused by *abducens palsy* (ie, palsy of the sixth cranial nerve) in isolation or association with other cranial nerve palsies (eg, Möbius syndrome).

Infantile exotropia is less common than esotropia. Like esotropia, exotropia manifests within the first 6 months after birth and is characterized by a large angle of deviation. Causes of infantile exotropia include trochlear palsy (ie, congenital third nerve palsy, a type of paralytic strabismus) and abnormalities of the bones of the orbit (eg, Crouzon syndrome).

Acquired Strabismus

Acquired strabismus may result from a variety of causes (Box 91.2). Accommodative esotropia and intermittent exotropia are the 2 most

common types of acquired strabismus. Accommodative esotropia typically manifests in children between 2 and 4 years of age but may occur as early as 6 months or as late as 8 years. Children with hyperopia use accommodation (ie, attempts to focus) to see clearly. The accommodative reflex is closely linked to convergence; when accommodation occurs, so does convergence. If children have severe hyperopia (ie, farsightedness), the amount of convergence that occurs with accommodation may be severe and may result in the development of esotropia. Such esotropia is usually intermittent initially and only gradually becomes constant. Often, the deviating eye becomes amblyopic.

Intermittent exotropia, which is the most common form of exodeviation in children, manifests between birth and 4 years of age. Although it begins as an intermittent condition in which the eyes appear to deviate outward, especially when a child is tired, ill, or fixating at a distance, the exotropia can become constant with time. A child also may close 1 eye in bright sunlight, presumably in an attempt to prevent diplopia.

Box 91.2. Differential Diagnosis of Strabismus

Congenital or Infantile Strabismus

Esophoria/Esotropia
- Infantile esotropia
- Pseudoesotropia
- Möbius syndrome
- Abducens palsy (ie, congenital sixth nerve palsy)
- Duane syndrome

Exophoria/Exotropia
- Congenital exotropia
- Trochlear palsy (ie, congenital third nerve palsy)
- Abnormalities of the bony orbit (eg, Crouzon syndrome)

Esophoria/Esotropia and Exophoria/Exotropia
- Duane syndrome (esotropia more common than exotropia)

Acquired Strabismus

Esophoria/Esotropia
- Accommodative esotropia
- Abducens palsy (benign sixth nerve palsy)

Exophoria/Exotropia
- Intermittent exotropia
- Overcorrection after surgery for esotropia

Esophoria/Esotropia and Exophoria/Exotropia
- Poor vision
- Orbital trauma causing entrapment of extraocular muscles
- Intracranial tumors or tumors involving the orbit (eg, retinoblastoma)
- Myasthenia gravis
- Central nervous system infection (eg, meningitis)
- Central nervous system tumor
- Orbital cellulitis

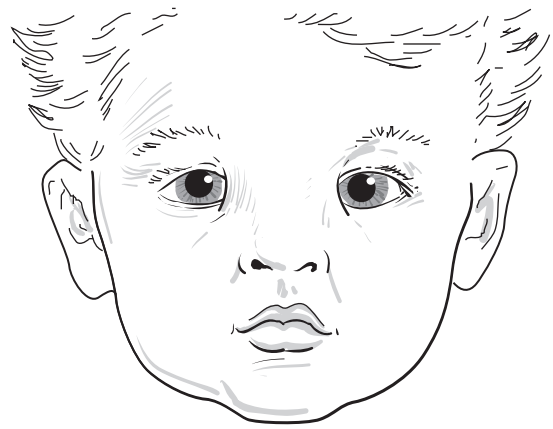

Figure 91.1. Illustration showing a child with pseudoesotropia. Note the wide nasal bridge and prominent epicanthal folds.

Evaluation

History

Evaluation of infants or children with suspected strabismus should begin with a thorough family history, because strabismus often runs in families (Box 91.3). Parental description of the ocular deviation is useful because misalignments, especially intermittent deviations that may manifest only when children are tired, may not always be evident during the office visit. A history of head or orbital trauma may help in the evaluation of acquired strabismus.

Physical Examination

On physical examination, the presence of any dysmorphic features and structural abnormalities of the face or neck (eg, torticollis) is noted. Children with paralytic strabismus (eg, trochlear palsy [ie, fourth nerve palsy], superior oblique palsy) may compensate for their paretic lesion by tilting the head to avoid diplopia. It is important that visual screening of children begin during the neonatal period. Newborn screening should emphasize the presence of a bilateral red reflex. An abnormal red reflex or a white reflex may be indicative of a cataract or retinoblastoma, both of which require immediate referral to an ophthalmologist. Evaluation for ocular alignment should begin at the 4-month health maintenance visit. Intermittent misalignment of the eyes is often seen in otherwise healthy infants younger than 4 months. Constant misalignment at any age, however, requires immediate attention.

Box 91.3. What to Ask

Suspected Strabismus
- Does the infant or child have a family history of strabismus?
- Does the infant or child constantly tilt the head toward one side?
- Does the infant or child squint?
- Has the infant or child reported blurred or double vision?
- Does the infant or child close 1 eye in bright sunlight?
- Has the infant or child incurred any recent trauma to the eyes or head?

Vision Testing

Testing visual acuity is essential in the evaluation of children with suspected strabismus. Such testing may be performed as early as 3 years of age if children are cooperative. Charts with symbols, figures, or letters can be used. The traditional Snellen chart with letters can generally be used in children as young as 4 years of age. Decreased vision in 1 eye may be indicative of ocular abnormalities, including ocular deviations.

The 2 basic tests for strabismus that can be easily performed in the office are the corneal light reflex test (ie, Hirschberg method) and the cover test. The pediatrician should be comfortable performing both tests.

The simplest and quickest test for the evaluation of strabismus is the *corneal light reflex test*, in which a penlight is projected simultaneously onto the corneas of both eyes as the child looks straight ahead. The examiner compares the placement of the corneal light reflex in each eye with respect to the center of the pupil. If the eyes are straight, the reflection appears symmetrically in the center of both pupils or on the same point on each cornea. If the light reflex appears off center in 1 eye compared with the other, the test is positive for ocular deviation or heterotropia. Nasal deviation of the light reflex on the cornea indicates exotropia on that side, temporal deviation signifies esotropia, and inferior deviation indicates hypertropia.

Unlike the corneal light reflex test, which may be performed even in uncooperative children, cover tests require a child's cooperation and ability to fixate on a specified object. These tests are used to detect heterophoria. Two types of cover test are used: the alternate cover test and the cover-uncover test. Only the alternate cover test detects both heterophoria and heterotropia. This test may be preferred by the primary care physician as a screening tool. The cover-uncover test detects only manifest deviation or heterotropia. In the *alternate cover test*, first 1 eye and then the other is covered as the child fixates on an object at a distance. If neither eye moves as the cover is moved rapidly between the eyes, the eyes are in alignment (ie, orthophoric). With heterotropia, the deviating eye moves when the fixating eye is occluded; in heterophoria, the deviating eye moves when it is uncovered (Figure 91.2).

The alternate cover test may be illustrated with the following example. A child presents with constant esotropia of the left eye. When the right or fixating eye is occluded, the left eye is forced to fixate so that the child can see, and the left eye moves outward as the right eye is occluded. In the case of a child with an esophoria or latent deviation of the left eye, the eye deviates inward when it is occluded because it is not being forced to fixate. As the cover is moved from the left eye to the right, the left eye moves outward and returns to a position of fixation.

The alternate cover test may be more difficult to interpret in children with bilateral or alternating strabismus who use both eyes in turn for fixation. It is not necessary for the pediatrician to identify exactly what type of strabismus is present. Rather, it is sufficient to note abnormal movement and refer the child for further evaluation. An ophthalmologist can perform a more detailed examination.

Management

The goals of management are the attainment of the best possible vision in each eye, straight eyes cosmetically, and fusion. The sooner deviations are corrected, the better the child's chances for equal

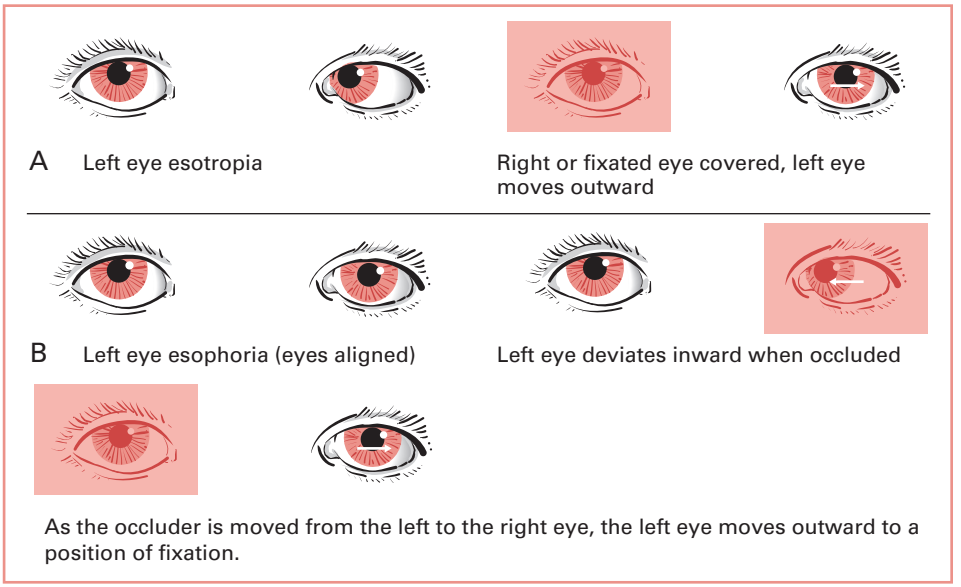

Figure 91.2. Alternate cover test in the detection of strabismus. Normally, both eyes appear to be aligned and centrally fixed. A, Detection of esotropia. The right eye is fixating, and a left esotropia is present. When the right or fixating eye is covered, the left eye moves outward (away from the nose). B, Detection of esophoria. The eyes are aligned with a left esophoria. When the left eye is covered, it deviates inward. As the cover is moved from the left eye to the right eye, the left eye moves outward to a position of fixation.

bilateral vision. Treatment includes correction of any underlying refractive error with corrective lenses. Such lenses, which remedy the refractive error and minimize the need for accommodation, are used in the management of accommodative esotropia. Glasses are also used in cases of anisometropic amblyopia in which the refractive error in 1 eye is significantly different from that in the other eye.

Children who do not see equally well from both eyes may be at risk for amblyopia if they preferentially fixate with only 1 eye. If detected, amblyopia should be corrected with occlusion therapy of the fixating "good" eye. Occlusion therapy forces children to use the amblyopic eye. This treatment is best accomplished by constantly patching the eye with better vision during waking hours or penalization with dilating drops in the better-seeing eye. Children require repeat evaluations and close monitoring during this therapy.

If eye alignment is not achieved nonsurgically, surgical correction may be necessary. Surgery may be used to achieve the best possible ocular alignment and is usually required for the management of infantile esotropia. It is generally performed in infants between 6 months and 1 year of age, while the visual system is still pliable enough to allow for the development of postoperative binocular vision. Surgery also may be needed in children with intermittent exotropia in whom the frequency of deviation is increasing.

Prognosis

Certain conditions, such as pseudoesotropia or infrequent intermittent exotropia, may resolve as children mature. Others, such as infantile esotropia, require early detection and management to achieve the best binocular vision. Amblyopia and permanent vision loss may result if correction of strabismus is delayed.

CASE RESOLUTION

The infant has pseudoesotropia. Although the boy's eyes appear to deviate, the corneal light reflex and cover tests are normal. Physical examination reveals prominent epicanthal folds and a broad, flat nasal bridge.

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CHAPTER 92

Infections of the Eye

Teresa O. Rosales, MD

CASE STUDY

A 10-day-old neonate has a 1-day history of red, watery eyes and nonproductive cough with no fever. She is breastfed and continues to eat well. She was the 3,232-g (7-lb, 2-oz) product of a term gestation, born via normal spontaneous vaginal delivery without complications to a 26-year-old woman. The pregnancy was also uncomplicated. No one at home is ill.

On examination, the infant is afebrile with normal vital signs. Examination of the eyes reveals bilateral conjunctival injection with only a mild amount of purulent discharge. Bilateral red reflexes are present. The remainder of the physical examination is within normal limits.

Questions

1. What is the differential diagnosis of conjunctivitis during and after the neonatal period?
2. What laboratory tests, if any, should be performed in neonates with conjunctivitis?
3. When is chest radiography indicated in the evaluation of the neonate with conjunctivitis?
4. What are management strategies for eye infection in older infants and children?

Infections of the eye and surrounding structures are commonly seen by pediatricians. Such infections range in severity from common problems, such as blepharitis and conjunctivitis, which lack serious sequelae, to severe and less common infections, such as periorbital and orbital cellulitis. The presenting concern in many children with eye infection is a red-appearing eye. Familiarity with the common causes of a red eye makes prompt diagnosis and treatment possible.

Epidemiology

Conjunctivitis, which affects children of all ages, is perhaps the most common eye infection of childhood. The rate of conjunctivitis in the newborn period is estimated to range from 1.6% to 12%. The prevalence of chlamydial conjunctivitis is approximately 8 in 1,000 live births. Approximately two-thirds of acute childhood conjunctivitis has a bacterial etiology, and one-third is viral. *Haemophilus influenzae* and *Streptococcus pneumoniae* are the most common bacterial agents and account for approximately 40% and 10% of culture-proven cases, respectively. The incidence of *H influenzae* is decreasing with the advent of the *H influenzae* type b vaccine. The incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing. *Staphylococcus aureus* is isolated from the conjunctivas of children with acute conjunctivitis, but it is found with approximately the same frequency in the eyes of children without conjunctivitis. Adenovirus is the most common viral isolate. Most cases of acute conjunctivitis in young adults have a viral etiology. Serious eye infections, such as periorbital and orbital cellulitis, occur far less often.

Clinical Presentation

Red eyes and discharge are the common presenting signs of infection of the eyelids and conjunctivas. Eyelid edema and erythema surrounding the eye characterize periorbital and orbital cellulitis. Proptosis, abnormal extraocular movement, or loss of visual acuity may signal spread of the infection beyond the orbital septum, as in orbital cellulitis (Box 92.1).

Pathophysiology

Eye infections may be divided into 2 types: those affecting the structures surrounding the orbit and those involving the orbital contents themselves (Figure 92.1). Although all structures surrounding the eye may potentially become inflamed or infected, the eyelids; nasolacrimal drainage system, as in dacryocystitis (see Chapter 93); conjunctiva; and cornea are most commonly involved. *Orbital cellulitis* is defined as an infection of the orbital structures posterior to the orbital septum. The orbital septum, an extension of the periosteum of the bones of the orbit, extends to the margins of the upper and lower eyelids and provides an anatomic barrier to the spread of most infectious and inflammatory processes. Preseptal or periorbital cellulitis is localized to structures superficial to the orbital septum, whereas postseptal or orbital cellulitis implies that the disease process involves orbital structures extending beyond the septum.

Differential Diagnosis

Infections of the eye are included in the differential diagnosis of conditions presenting with red eye (Box 92.2). Also included in the differential diagnosis are congenital, inflammatory, traumatic, and

Box 92.1. Diagnosis of Eye Infection

Eyelid Infections
- Redness
- Itching (blepharitis)
- Burning (blepharitis)
- Scales at the base of the lashes (seborrheic blepharitis)
- Swelling (hordeolum or chalazion)
- Pain (hordeolum)

Conjunctivitis
- Conjunctival injection and edema
- Excessive tearing
- Discharge or crusting
- Itching (allergic conjunctivitis)

Uveitis
- Conjunctival injection
- Pain
- Blurred vision
- Photophobia
- Headache

Periorbital Cellulitis
- Unilateral eyelid edema
- Erythema surrounding the eye
- Pain
- Fever

Orbital Cellulitis
- Eyelid edema
- Proptosis
- Decreased extraocular movements
- Loss of visual acuity
- Fever
- Ill appearance
- Associated sinusitis

Box 92.2. Differential Diagnosis of Red Eye

Congenital Anomalies
- Nasolacrimal duct obstruction
- Congenital glaucoma

Infection
- Keratitis
- Conjunctivitis
- Dacryocystitis
- Corneal ulcer
- Periorbital and orbital cellulitis

Inflammation
- Blepharitis
- Hordeolum
- Chalazion

Trauma
- Corneal abrasion
- Foreign body
- Blunt trauma: hyphema
- Perforating injuries
- Exposure to chemicals or other noxious substances

Systemic Illnesses
- Kawasaki disease
- Varicella
- Measles
- Lyme disease
- Stevens-Johnson syndrome
- Ataxia-telangiectasia
- Juvenile rheumatoid arthritis

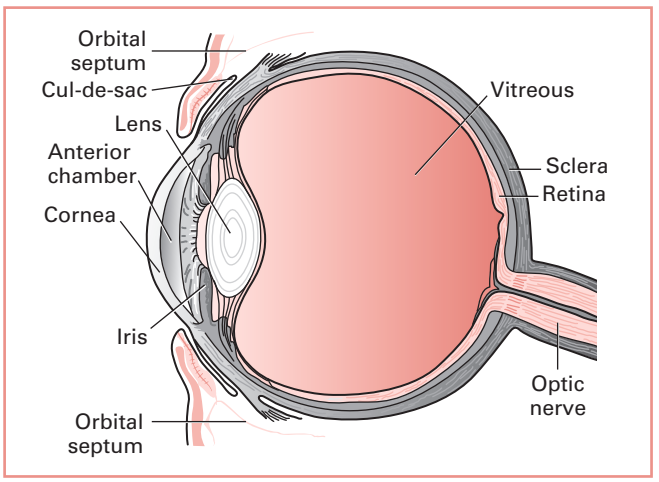

Figure 92.1. The eye and surrounding structures.

systemic processes. Although infection and irritation are by far the most common causes of an acute onset of red eye, other possibilities, including trauma, glaucoma, or underlying systemic disease, must be considered.

Eyelid Infections

Common conditions affecting the eyelid and its related structures are blepharitis, hordeolum, and chalazion.

Blepharitis is an inflammation of the lid margins. This condition, which is often bilateral, may be chronic or recurrent. The 2 most common causes of blepharitis are staphylococcal infection and seborrheic dermatitis. The child with staphylococcal blepharitis often presents with scales at the base of the lashes, ulceration of the lid margin, and loss of lashes. The infection may spread to the conjunctiva or cornea, producing conjunctivitis or keratitis. In contrast, seborrheic blepharitis is characterized by greasy, yellow scales attached to the base of the lashes. Additionally, associated seborrhea of the scalp or eyebrows may be present. Mixed staphylococcal-seborrheic infections, which occur as staphylococcal superinfection, may complicate seborrheic blepharitis. Less commonly seen forms

of blepharitis are parasitic blepharitis, which results from infestation of the lids by the head louse, *Pediculus humanus capitis,* or crab louse, *Phthirus pubis,* and primary or recurrent human herpesvirus 1 infections that may manifest as clusters of vesicles on the eyelids. Rosacea may rarely occur in childhood and can present very similarly to chronic blepharitis.

The glands of the eyelid can also be infected. *Staphylococcus aureus* is the most common organism. A *hordeolum*, or common *stye*, results from an infection of the meibomian glands located along the lid margins. The glands become obstructed and an abscess can form. The affected child presents with a well-circumscribed, painful swelling that may be at the lid margin or deeper in the lid tissue. These generally rupture or resolve without complications when managed aggressively with hot compresses.

A *chalazion* is a hordeolum that has not resolved over weeks to months. It is no longer an infectious process but has become a chronic granulomatous inflammation of the meibomian glands. The resulting firm, nontender, slow-growing mass within the upper or lower eyelid may be painful if secondary infection is present.

Infections of the Conjunctiva

Conjunctivitis refers to any inflammation of the conjunctiva. The condition may be allergic, chemical, viral, or bacterial in etiology. Additionally, it may be a sign of systemic disease, such as Kawasaki disease or Stevens-Johnson syndrome.

Acute conjunctivitis, or pinkeye, is common during childhood and can be extremely contagious. The usual signs are conjunctival injection, tearing, discharge, crusting of the lashes, and conjunctival edema (ie, chemosis). Pain and decreased vision are uncommon symptoms and may signal corneal involvement.

Generally, it is difficult to distinguish bacterial conjunctivitis from viral conjunctivitis on clinical features alone. Certain clinical characteristics may guide the diagnosis. The average age of children affected with bacterial conjunctivitis tends to be younger than the age of those with viral conjunctivitis, which occurs more frequently in adolescents; however, considerable overlap occurs. The child with bacterial conjunctivitis typically presents with an acute onset of unilateral or bilateral injection and edema of the palpebral and bulbar conjunctiva, minimal to copious purulent discharge, and crusting of the eyelashes. The child may have difficulty opening the eyes on awaking in the morning because of the exudate. An association between conjunctivitis and concomitant otitis media has been well described. *Haemophilus influenzae,* which is often resistant to ampicillin, is the pathogen most commonly isolated from affected children.

The diagnosis of viral conjunctivitis is considered if signs of viral upper respiratory infection (eg, low-grade fever, cough, rhinorrhea) are evident. Viral infection is associated with conjunctival injection, watery or thin mucoid discharge, and only mild lid edema and erythema. Adenoviral infection is usually bilateral, with significant conjunctival injection and chemosis of the conjunctiva, and is often accompanied by a tender preauricular lymph node. Epidemic keratoconjunctivitis is a highly contagious form of adenoviral conjunctivitis. Affected children often report foreign body sensation beneath the lids or photophobia resulting from corneal involvement. Pharyngeal conjunctival fever, another presentation of adenoviral conjunctivitis, usually manifests as conjunctivitis in association with pharyngitis and fever.

The infant with chronic or recurrent conjunctival discharge may have an obstruction of the nasolacrimal duct, whereas the older child with chronic conjunctivitis may have allergic disease, recurrent blepharitis, or chlamydial infection. Blepharitis is the most common cause of chronic conjunctivitis in older children. *Staphylococcus aureus* is frequently implicated in these infections.

Itching, tearing, and conjunctival edema are the hallmarks of *allergic conjunctivitis*, a noninfectious form of conjunctival inflammation often occurring in children with other allergic disorders, such as asthma or hay fever. Conjunctival injection tends to be mild, bilateral, and seasonal. The etiology is most often a hypersensitivity to pollens, dust, or animal dander. Vernal conjunctivitis is a bilateral, severe form of allergic conjunctivitis seen primarily during childhood. Most cases occur during the spring and summer. Severe itching and tearing are the most frequent complaints. The palpebral conjunctiva may have a cobblestone appearance resulting from the accumulation of inflammatory cells, or there may be small, elevated lesions of the bulbar conjunctiva at the corneal limbus. The pathogenesis is unclear, but atopy seems to play a role.

Chlamydial conjunctivitis frequently affects neonates and adolescents. Inclusion conjunctivitis is an acute infection of the eyes caused by sexually transmitted *Chlamydia trachomatis* (usually serotypes D–K). This condition may be seen in the neonate or sexually active adolescent. Trachoma, the most common cause of impaired vision and preventable blindness worldwide, is a chronic conjunctivitis usually caused by *C trachomatis* serotypes A, B, and C. Although this disease is rarely seen in North America, it is endemic among certain populations, especially Native Americans. Inclusion conjunctivitis and endemic trachoma are characterized initially by conjunctivitis with small lymphoid follicles in the conjunctiva.

Neonatal conjunctivitis, or ophthalmia neonatorum, occurs during the first month after birth. In decreasing order of frequency, the major causes of neonatal conjunctivitis are chemical, chlamydial, and bacterial. Ophthalmia neonatorum may be produced by the same bacteria that cause childhood conjunctivitis but also results from organisms such as *C trachomatis* and *Neisseria gonorrhoeae.* The newborn may acquire these latter pathogens following premature rupture of membranes or passage through an infected or colonized birth canal. *Chlamydia trachomatis* is the organism most commonly identified. It has been isolated from 17% to 40% of neonates with conjunctivitis. The neonate born to a mother with active cervical chlamydial infection has a 20% to 50% chance of developing chlamydial conjunctivitis. Viruses are uncommon causes of neonatal ocular infections. Human herpesvirus is the primary viral agent involved in neonatal conjunctivitis. The presence of characteristic vesicular skin lesions or corneal dendritic lesions helps in the diagnosis.

Time of onset of symptoms is related to the etiologic agent. Inflammation secondary to the silver nitrate drops instilled at birth to prevent gonococcal infection presents as mild conjunctivitis 12 to 24 hours after birth in 10% to 100% of treated newborns. This condition usually resolves spontaneously in 24 to 48 hours. This is more of historic interest because erythromycin ointment 0.5% has replaced silver nitrate in most hospitals. (Silver nitrate was ineffective against *C trachomatis.*) Conjunctivitis resulting from *N gonorrhoeae* appears 2 to 5 days after birth and is associated with copious purulent discharge. Conjunctivitis caused by *C trachomatis* occurs at 5 to 14 days, a result of a longer incubation period. Time of onset and severity of symptoms of these 2 conditions may overlap, however. The presentation of gonococcal infection may be delayed for 5 days or more because of the partial suppression of the infection by the prophylactic drops instilled at birth. Chlamydial infection can vary in severity from mild erythema of the eyelids to severe inflammation and copious purulent discharge. Chlamydial infection is primarily localized to the palpebral conjunctiva and only rarely affects the cornea. Gonococcal conjunctivitis is considered a medical emergency because the gonococcus can penetrate the cornea, resulting in corneal ulceration and perforation of the globe within 24 hours if untreated.

Concomitant nasopharyngeal chlamydial infection is common. Spread of the organism from the nasopharynx to the lungs is a sequela of colonization. Ten percent to 20% of newborns and infants with conjunctivitis have chlamydial pneumonia. It may occur simultaneously with the conjunctivitis or up to 4 to 6 weeks later. The affected newborn or infant usually is afebrile and presents with symptoms of increasing tachypnea and cough.

Anterior uveitis may be confused with conjunctivitis. The uvea consists of the iris, ciliary body, retina, and choroid. Inflammation of the iris or ciliary body may produce conjunctival injection, which may be associated with decreased visual acuity, pain, headache, and photophobia. Systemic conditions associated with uveitis include Kawasaki disease, juvenile idiopathic arthritis, Lyme disease, tuberculosis, sarcoidosis, *Toxocara* infection, toxoplasmosis, and spondyloarthropathies.

Infections of the Eye and Surrounding Tissues

Preseptal cellulitis and orbital cellulitis are 2 serious infections of the eyelids and surrounding structures. Although these infections are not as frequent as those that are limited to the eye, they have serious sequelae. The preseptal space is defined by the skin of the eyelid on one side and the orbital septum on the other. The child with preseptal cellulitis, or periorbital cellulitis, usually presents with acute onset, unilateral upper and lower eyelid edema, erythema, and pain. The condition is often associated with systemic signs and symptoms, such as ill appearance, fever, and leukocytosis. The eye itself usually appears normal. Infection may follow hematogenous seeding of the preseptal space, most often with *H influenzae* type b or *S pneumoniae,* or after traumatic breaks in the skin that usually result in *S aureus* infection.

Orbital cellulitis is an infection of the contents of the orbit posterior to the orbital septum. Usually an insidious onset of eyelid edema, proptosis, decreased extraocular movements, and loss of visual acuity occur. As with periorbital cellulitis, the affected child is often febrile and ill-appearing. Contiguous spread of infection from adjacent sinusitis (most often ethmoid) is the most common cause. The organisms most often involved are the same as those in acute sinusitis (ie, *S aureus, S pneumoniae,* non-typeable *H influenzae*). Untreated, the infection may progress to orbital abscess formation or progress posteriorly in the orbit to the cavernous sinus and brain.

Primary human herpesvirus infection can affect the skin surrounding the eyes as well as the eye itself. Most of these infections are caused by human herpesvirus 1, although human herpesvirus 2 infections may occur in the newborn. The child with herpetic infection of the eye usually presents with unilateral skin vesicles and a mild conjunctivitis or keratitis. Herpetic keratoconjunctivitis can recur after fever, exposure to sunlight, or mild trauma. The characteristic corneal lesion of herpetic keratitis is the dendritic corneal ulcer, which appears as a tree branch pattern on fluorescein staining of the cornea. Although this lesion may occur with primary infection, it is more common in recurrent infections. Skin vesicles may not appear with a recurrence, which makes it difficult to distinguish herpetic infection from other causes of conjunctivitis. Steroids may cause progression of the herpetic infection and permanent corneal scarring as well as cataracts and glaucoma. Empiric topical steroid treatment for presumed viral conjunctivitis should be avoided for this reason. Neonatal herpetic infections of the eye primarily result from human herpesvirus 2. Infections may be isolated to the eye, or the eye may be infected secondarily resulting from central nervous system or disseminated disease. Proper diagnosis is important because disseminated herpetic disease has a mortality rate of approximately 85%, and central nervous system disease has a mortality rate of 50%. Isolated herpetic eye disease is quite rare in neonates.

Evaluation

History

A careful history taken from the parent or primary caregiver as well as the child can guide the diagnosis (Box 92.3). It is important to exclude the possibility of ocular trauma or exposure to noxious chemicals when evaluating the child with red, irritated eyes.

Physical Examination

A thorough examination of the eyes should be performed. The eyelids, conjunctiva, and cornea should be inspected for evidence of inflammation or foreign bodies. The presence of any discharge or crusting of the eyelids as well as light sensitivity or pain should be noted. Extraocular movements should be checked, and their symmetry should be noted. Visual acuity should be determined, and an ophthalmoscopic examination of the retina should be performed whenever possible. A slit-lamp examination of the eye is indicated if uveitis is suspected. Additionally, it is important to perform a thorough head and neck examination, noting the

Box 92.3. What to Ask

Eye Infections

- How long has the child had symptoms?
- Is the child having any difficulty seeing clearly?
- Is the child reporting light sensitivity?
- Has the child had fever, cold symptoms, or purulent nasal discharge (eg, green, yellow)?
- Are the eyes pruritic (ie, itchy) or painful?
- Does the child have difficulty opening the affected eye on awaking in the morning or after naps?
- Has the parent or guardian noticed any discharge from the eyes or crusting around the eyelids?
- Is the child reporting earache or sore throat?
- Does the child have allergies, asthma, or hay fever?
- Has any trauma or bug bites occurred?

presence of associated sinusitis, otitis media, pharyngitis, or preauricular nodes.

Laboratory Tests

Laboratory assessment is guided by the history and physical examination. Although clinical differentiation between a bacterial and viral etiology is difficult, cultures usually are not required because acute conjunctivitis in children is a self-limited disease. In neonatal conjunctivitis, however, the time of onset of illness and clinical findings overlap, and Gram stain and cultures are essential. Gonococcal infection is assessed by Gram stain and culture. Treatment may be initiated on the basis of Gram stain alone because of the serious potential for corneal involvement and subsequent loss of visual acuity.

If human herpesvirus is suspected, viral cultures should be obtained. If chlamydial infection is suspected, a nasopharyngeal culture should be sent in addition to conjunctival scraping. Purulent material may be examined for gonococci, but conjunctival scrapings are required for chlamydia because chlamydia is an obligate intracellular organism. Laboratory assessment of periorbital cellulitis includes a complete blood cell count, blood culture, and a lumbar puncture in the young infant or child with signs of meningeal irritation. The reported prevalence of meningitis is 1% in children with periorbital cellulitis and 10% in children with bacteremia and periorbital cellulitis. As with periorbital cellulitis, laboratory assessment of orbital cellulitis includes a complete blood cell count and blood culture.

Imaging Studies

Imaging studies are required infrequently in the assessment of eye infections. Chest radiography to detect pneumonia should be obtained if the infant with neonatal conjunctivitis has respiratory symptoms. Characteristic features on chest radiography include hyperinflation and diffuse or patchy interstitial infiltrates. In orbital cellulitis, computed tomography of the orbit and sinuses may be useful for assessing the degree of involvement.

Management

Most common eye infections resolve spontaneously or respond readily to hygiene and topical antibiotics. Treatment of staphylococcal and seborrheic blepharitis consists of daily lid hygiene (usually at bedtime), including application of a warm compress and removal of the scales and crusts with a moistened, warm washcloth. The eyelashes and lid margins may also be scrubbed with a washcloth soaked in a 50:50 mixture of baby shampoo and water. When staphylococcal blepharitis is present, an ointment containing an anti-staphylococcal antibiotic agent, such as erythromycin, may be applied to the eyelids after cleansing. Treatment of parasitic blepharitis consists of application of petrolatum ophthalmic ointment (to smother the nits) several times a day for 1 week, followed by removal of the remaining parasites and their ova with tweezers or forceps.

Treatment for hordeola consists of application of hot compresses several times a day. This usually causes the abscess to come to a point and drain. Occasionally, surgical excision and drainage may be required if the abscess does not resolve. Unlike the hordeolum, a chalazion generally requires surgical excision because spontaneous resolution is uncommon.

Most cases of acute childhood conjunctivitis can be managed successfully by the primary care physician. Acute conjunctivitis in childhood is generally a self-limited disease. However, antibiotic treatment of bacterial conjunctivitis hastens recovery and may help prevent secondary cases by eradicating the bacterial pathogen. It is helpful to determine clinically whether the infection is bacterial and initiate empiric treatment with topical antibiotic preparations. Trimethoprim and polymyxin B sulfate (eg, Polytrim), sodium sulfacetamide (eg, Bleph-10, Sodium Sulamyd), gentamicin (eg, Garamycin, Gentak), tobramycin (eg, Tobrex), and moxifloxacin (eg, Vigamox) are some of the commonly prescribed antibiotics. Trimethoprim and polymyxin B sulfate as well as gentamicin remain highly effective against MRSA. Neomycin-containing products should be avoided, because sensitivity to neomycin occurs frequently. Antibiotic ointments may be easier to instill in the infant or young child. Antibiotic drops should be used in the older child during the day because the ointments can blur the vision; ointments may be used at bedtime. Systemic therapy can be considered for concomitant conjunctivitis and otitis media. Good hygiene with special attention to handwashing is important to prevent the spread of the infection to the other eye as well as family and friends. Even if the child is on antibiotic drops, the child should not go to school until the discharge and drainage have resolved. If symptoms persist for more than 7 to 10 days or if the diagnosis is in question, appropriate cultures should be taken. Immediate referral to an ophthalmologist is required for complicated cases, such as suspected herpetic, gonococcal, or MRSA infection; foreign bodies that cannot be removed easily; loss of visual acuity; presence of significant pain; those involving a history of recent penetrating ocular trauma or surgery; and those involving contact lens use. Contact lens wearers with red eyes are at high risk for corneal ulcers. They should be instructed to leave their lenses out until seen by the ophthalmologist.

Allergic conjunctivitis can be managed with cool compresses. Topical decongestant or antihistamine drops drops may provide symptomatic relief if treatment is indicated. Vernal conjunctivitis may be managed with topical cromolyn sodium drops or medications designed to relieve redness and itching and stabilize mast cells, such as olopatadine hydrochloride (eg, Patanol, Pataday) or ketorolac tromethamine (eg, Toradol, Acular). Caution should be used when prescribing corticosteroid preparations for the eye because they may cause progression of an undiagnosed herpetic eye infection. Chronic use of topical steroids can cause cataracts and glaucoma.

Management of neonatal conjunctivitis depends on the diagnosis. If gonococcal infection is suspected and Gram stain result is positive for gram-negative diplococci, immediate parenteral therapy with ceftriaxone should be initiated. Chlamydial conjunctivitis should be managed with systemic rather than topical treatment to prevent systemic disease. Oral erythromycin is the drug of choice. Although oral treatment provides adequate local antibiotic levels, topical erythromycin ointment may be used in conjunction with systemic therapy to provide more prompt relief of ophthalmic symptoms. The parent(s) or guardian(s) should also be treated.

Empiric parenteral antibiotic therapy (eg, cefuroxime) should be initiated for periorbital cellulitis. Repeat evaluations for signs of progression should be performed frequently during the initial 24 to 48 hours. If orbital cellulitis is suspected, an ophthalmologist should be consulted, and hospitalization and systemic antibiotics should be instituted. Surgical drainage of the sinuses or an orbital abscess is sometimes necessary.

The child with suspected herpetic infection should be referred to an ophthalmologist. Intravenous acyclovir is often recommended for the management of isolated herpetic eye infections in the neonate.

Prognosis

Most common eye infections, such as blepharitis, hordeolum, and acute childhood conjunctivitis, resolve without sequelae. Recurrence is common for hordeola, and periorbital cellulitis may be a potential complication in rare or untreated cases. Unlike acute conjunctivitis, chronic conjunctivitis may not be self-limited. Appropriate diagnosis and management are extremely important to prevent serious sequelae in some children. For example, endemic trachoma may progress to produce conjunctival scarring, pannus formation, and even blindness if not appropriately managed with systemic erythromycin or tetracycline. (Generally, systemic tetracycline should not be used in the child younger than 8 years to avoid discoloration of the teeth.)

Periorbital cellulitis generally resolves without sequelae if treated promptly with systemic antibiotics. Orbital cellulitis should be considered a true ophthalmologic emergency because the potential for complications is high. The optic nerve may become involved, resulting in loss of vision or spread of the infection into the cranial cavity. This spreading may result in meningitis, cavernous sinus thrombosis, or brain abscess.

CASE RESOLUTION

The newborn has neonatal conjunctivitis. A Gram stain of the purulent discharge should be examined, and cultures should be taken from the eye and nasopharynx. If the Gram stain result is negative for gonococci, empiric treatment for chlamydia may begin with oral erythromycin.

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CHAPTER 93

Excessive Tearing

Teresa O. Rosales, MD

CASE STUDY

A 4-week-old girl has had a persistent watery discharge from both eyes since birth. Her mother has noticed white, crusty material on her daughter's eyelids for the past few days. The infant's birth and medical history are unremarkable. Examination of the eyes, including bilateral red reflexes and symmetric extraocular movements, is normal, except that the left eye appears "wetter" than the right.

Questions

1. What is the differential diagnosis of excessive tearing in infancy?
2. How do physical findings such as corneal enlargement and haziness influence the differential diagnosis?
3. How should excessive tearing in infants be managed?
4. When should a child with excessive tearing be referred to an ophthalmologist?

Excessive tearing or epiphora in 1 or both eyes in infants or young children is a common pediatric ophthalmologic concern. The pediatrician must be capable of differentiating benign causes of this common childhood condition from more serious illnesses (eg, glaucoma) that have the potential to threaten vision.

Obstruction of the Nasolacrimal Duct

Epidemiology

Dacryostenosis, that is, congenital obstruction of the nasolacrimal duct (NLD), occurs in 1% to 6% of newborns and infants and is the most common cause of excessive tearing in infancy. Eighty percent of cases of dacryostenosis resolve spontaneously by 6 months of age.

Clinical Presentation

Infants with dacryostenosis typically present with a history of a mucoid discharge and crusting along the eyelid margins. The affected eye appears "wetter" than the normal eye, and a small pool of tears may be noted along the lower eyelid. Frequent tearing is reported. Commonly, the patient has repeated episodes of infection with purulent discharge (Box 93.1).

Pathophysiology

The lacrimal system produces and drains tears away from the eyes and into the nose (Figure 93.1). Typically, reflex tearing is present shortly after birth; however, it may be delayed for several weeks to months until the lacrimal gland begins to function. Tears drain away from the eyes through the superior and inferior puncta into the superior and inferior canaliculi and finally into the NLD, which drains beneath the inferior turbinate into the nose.

Outflow obstruction, which typically results from dacryostenosis, is the most common cause of excessive tearing in infancy. The obstruction is usually bilateral and occurs during fetal development. Most commonly, a persistent, thin membrane (Hasner membrane) obstructs the opening of the sac in the nose. Typically, the membrane is located in the distal or nasal segment of the duct rather than the proximal portion. The term *dacryocystitis* is used in cases in which acute infection or inflammation is associated with the obstruction. If the canaliculi and NLD are obstructed, a dacryocystocele involving the nasolacrimal sac may be noted at birth. This sac appears as a bluish, firm mass located over the lacrimal sac. Atresia of some portion of the drainage system is an extremely rare occurrence. Infants with dacryocystocele, who have large intranasal cysts, may present with respiratory symptoms because infants are obligate nasal breathers. Symptoms range from difficulty during feeding (caused by obstruction of the mouth) to respiratory distress.

Differential Diagnosis

Box 93.2 outlines the differential diagnosis of excessive tearing in infancy. Although obstruction of the NLD is the most common cause of excessive tearing in newborns and infants, it is important to consider and rule out glaucoma when evaluating neonates and infants with excessive tearing. Infantile glaucoma may be unilateral or bilateral.

Acute onset of excessive tearing in older children is usually the result of ocular irritation. Any irritation of the conjunctiva, cornea, or eyelids may produce tearing. Conjunctivitis and corneal abrasion (secondary to a foreign body in the eye or human herpesvirus keratoconjunctivitis) are the 2 most common causes. Eye infections are discussed in Chapter 92.

Evaluation

History

Evaluation of excessive tearing begins with a thorough patient history. The nature of any discharge (eg, watery, mucoid, purulent) is noted.

Box 93.1. Diagnosis of Excessive Tearing

- Conjunctival edema or injection
- Crusting of the eyelids
- Rhinorrhea
- Photophobia
- Corneal haziness
- Reflux of tears with gentle pressure on the medial canthus
- Wetness of the eye

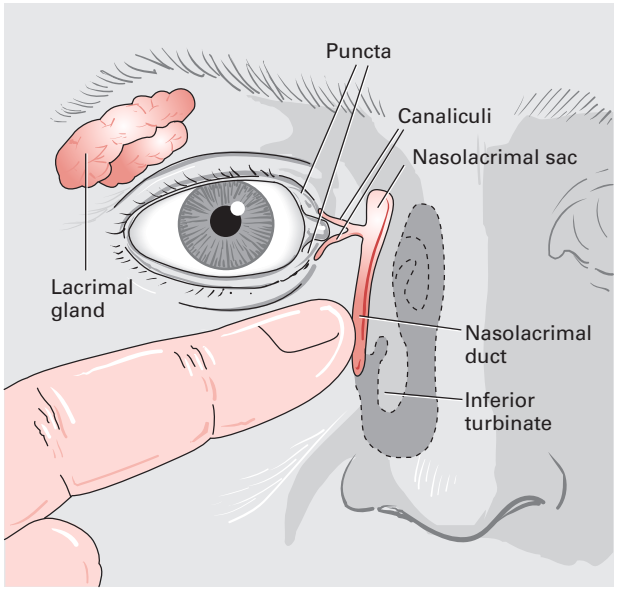

Figure 93.1. The lacrimal system, showing massage of the lacrimal sac (ie, Crigler massage).

Box 93.2. Differential Diagnosis of Excessive Tearing in Newborns and Infants

Increased Production

- Infantile glaucoma
- Allergy
- Conjunctivitis
- Corneal abrasion
- Foreign body under the eyelid

Outflow Obstruction

- Obstruction of the nasolacrimal duct (ie, dacryostenosis)
- Anomalies of the lacrimal drainage system
- Mucocele of the lacrimal sac
- Atresia of the lacrimal punctum or canaliculus
- Nasal congestion
- Craniofacial anomalies involving the midface

Parents or other caregivers should be questioned about the appearance of the infant's eyes (Box 93.3). The excessive mucoid discharge in the medial canthal region and on the eyelashes is noticeable to the family, as is the increased tearing. Crusting along the eyelashes caused by drying of the mucoid material is usually noted when infants awake in the morning or after a nap. Mucopurulent discharge may be noted if an associated acute infection is present (eg, dacryocystitis).

Physical Examination

A careful examination of the eyes in infants includes inspection, evaluation of extraocular movements, and funduscopic examination. While funduscopic examination may be difficult in this age group, it is easy to elicit bilateral red reflexes. Signs of dacryostenosis, which usually appear days to weeks after birth, include tearing, mucoid discharge, and crusting of the eyelids. Tearing may be as mild as an increased wetness of the affected eye; this is best evaluated prior to disturbing the infant. Visible overflow of tears from the affected eye is not unusual and is typically seen when the eye is irritated (eg, from cold or wind). Infants with dacryostenosis may present with associated erythema and edema of the eyelids as well. Dacryocystitis may also spread to the surrounding tissues, producing a periorbital cellulitis; systemic signs of infection, such as fever, may be noted. Gentle pressure along the medial canthal region over the lacrimal sac may produce a reflux of tears or mucoid discharge onto the surface of the eye, thus confirming the diagnosis of obstruction.

Laboratory Tests

Typically, routine laboratory assessment is not necessary.

Management

Early treatment of dacryocystoceles before 13 months of age is advised to prevent complications related to infection or respiratory distress. Digital massage may be attempted to decompress the dacryocystocele; occasionally, the condition resolves without surgery. Dacryocystoceles associated with acute respiratory distress require immediate surgical intervention.

Nasolacrimal duct probing alone may be curative; however, in approximately 25% of patients the condition persists after probing.

Box 93.3. What to Ask

Excessive Tearing

- How old was the infant when the excessive tearing began?
- Does the condition affect 1 eye or both eyes?
- How does the eye appear? How has its appearance changed?
- Is there a family history of infantile glaucoma?
- Does the infant have photophobia or light sensitivity (eg, closes eyes in bright sunlight)?
- Has the infant had any persistent, watery discharge?
- Does the infant have difficulty opening the affected eye on awaking in the morning or after a nap?

Nasolacrimal duct probing in conjunction with nasal endoscopy and intranasal cyst removal is effective in more than 95% of infants.

Spontaneous resolution of dacryostenosis is common by 6 to 8 months of age. The primary medical treatment of uncomplicated NLD obstruction consists of local massage and cleansing, beginning when symptoms are noted. Parents are instructed to massage the NLD several times a day by applying firm, downward pressure over the medial canthal region with a finger and sliding the finger down toward the mouth (ie, *Crigler massage*; Figure 93.1). This maneuver is done in an attempt to move fluid trapped within the nasolacrimal sac down through the duct to break the obstruction with hydrostatic pressure. Parents may be asked to cleanse the eyes with warm water before performing this maneuver. Antibiotic ointments and drops should be prescribed only if the discharge is purulent or associated conjunctivitis is evident.

Controversy exists about when probing of the NLD should be performed. Some ophthalmologists prefer probing the duct before infants are 6 months of age, because before this age the procedure may be performed in the office without general anesthesia. Other ophthalmologists state that more than 80% of obstructions resolve with conservative medical management by 6 months of age and prefer to delay probing until 9 to 12 months of age. At this age, however, the procedure must be performed under general anesthesia. Deciding when to proceed with probing depends on the standard of practice within the community, severity of symptoms, response to medical management, and level of parental concern.

Ophthalmologic referral is necessary for affected infants by 6 months of age if the obstruction has not resolved. Referral should be made sooner if symptoms are severe or infections recur.

Prognosis

Most cases of dacryostenosis resolve spontaneously by age 1 year without further sequelae. Tear duct probing, should it be necessary, is 90% to 95% successful if performed before 13 months of age. The success rate drops to 70% between 13 and 15 months of age and to 50% in those older than 18 months.

Congenital Glaucoma

Epidemiology

Congenital or infantile glaucoma, which is a serious cause of excessive tearing, is rare, with a prevalence of approximately 1 in 10,000 live births. Although glaucoma may be present at birth, onset during the first few weeks to months after birth is more common. Approximately 25% of cases are diagnosed at birth, and 80% of cases are diagnosed by 1 year of age. The severity of the disease is worse with earlier onset. Most affected infants are male; the male to female ratio in older infants is 2:1. Infantile glaucoma seems to have a multifactorial inheritance pattern, but most cases are sporadic. In families with 1 affected infant or a parental history of infantile glaucoma, the chance of having an infant with glaucoma is approximately 5%. Although glaucoma may be unilateral or bilateral, 75% to 90% of infants who present before 3 months of age have bilateral glaucoma.

Clinical Presentation

In addition to excessive tearing, other clinical signs of infantile glaucoma include *blepharospasm* (ie, spasmodic blinking of the eyelids), photophobia, corneal enlargement and corneal haziness resulting from corneal edema, progressive enlargement of the eye (ie, *buphthalmos*), and cupping and atrophy of the optic nerve (Box 93.1).

Pathophysiology

Glaucoma is the most serious and potentially sight-threatening etiology for excessive production of tears. *Glaucoma* refers to an increase in intraocular pressure that is severe enough to damage the eye and alter vision. In infants and children, glaucoma usually is a result of a developmental abnormality of the iridocorneal angle, which interferes with drainage of aqueous humor from the anterior chamber. Young infants differ from adults in that the globe in infants' eyes is distensible; the increased intraocular pressure not only produces corneal enlargement and edema but also expands the globe itself. Breakdown of the corneal epithelium and resultant irritation of the eyes produce reflex tearing and photophobia. Untreated glaucoma may result in optic nerve damage with resultant loss of visual acuity, decreased visual field, and even blindness. Glaucoma in children younger than 3 years of age is referred to broadly as *infantile glaucoma*, and glaucoma that occurs in children between 3 and 20 years of age is called *juvenile glaucoma*. Infantile glaucoma is further classified as primary or secondary. *Primary glaucoma* refers to isolated abnormalities of the iridocorneal angle, whereas *secondary glaucoma* may be associated with other ocular or systemic diseases. Juvenile glaucoma is a form of open-angle glaucoma.

Differential Diagnosis

Excessive tearing may be caused by increased production or outflow obstruction (see Box 93.2). Infants with increased production of tears demonstrate rhinorrhea in association with epiphora, a finding that distinguishes glaucoma from dacryostenosis. Rhinorrhea is not associated with dacryostenosis because the NLD is obstructed and no tears drain out the nose. Ocular irritation, which occurs with conjunctivitis, corneal abrasion, or a foreign body under the eyelid, also can produce excessive tearing, especially in older children. In addition, allergies are associated with excessive tearing resulting from overproduction.

Disorders associated with outflow obstruction include dacryostenosis, anomalies of the lacrimal drainage system (eg, dacryocystocele of the lacrimal sac, atresia of the lacrimal punctum or canaliculus), nasal congestion, and craniofacial anomalies involving the midface.

Evaluation

A corneal diameter greater than 12 mm in infants is suggestive of infantile glaucoma. Corneal edema is more common in newborns and in infants younger than 3 months and may cause the red reflex to appear dull in the affected eye. The optic cup may be enlarged. A cup to disk ratio greater than 0.3 or an asymmetry of the ratio between the eyes may be indicative of glaucoma.

As in adults, loss of visual fields occurs in children with glaucoma. Visual fields are difficult to evaluate in infants and young children because of their inability to cooperate with the examination.

Management

Suspected cases of glaucoma should be referred to an ophthalmologist immediately for further evaluation, including measurement of intraocular pressure. Pressures greater than 20 mm Hg are suggestive of glaucoma. (In persons of any age, normal intraocular pressure is 10 to 20 mm Hg.)

Surgery is the primary treatment for glaucoma. The goal is to normalize intraocular pressure and minimize irreversible damage to the cornea and optic nerve.

Prognosis

Left untreated, infantile glaucoma may progress to blindness. The visual prognosis depends on several factors, including age at onset, with the earlier the onset, the worse the prognosis; the amount of optic nerve damage; and the degree of myopia caused by the enlargement of the eye. In addition, amblyopia secondary to deprivation resulting from corneal opacities or unequal refractive errors is often seen (see Chapter 91).

CASE RESOLUTION

The infant has dacryostenosis. At this stage, it can be managed with medical treatment, such as local massage and cleansing. If her symptoms persist beyond age 6 months, consultation with an ophthalmologist is recommended.

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CHAPTER 94

Neck Masses

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CASE STUDY

A 2-year-old boy is brought to the office with a 1-day history of an enlarging red, tender "bump" beneath his right mandible. He has a fever (temperature 38.7°C [101.6°F]) and sores around his nose, upper lip, and cheek. These sores have been present for 3 days and have not responded to an over-the-counter antibiotic ointment. He had an upper respiratory tract infection 1 week previously, which has almost entirely resolved. He is otherwise in good health. The family has no history of tuberculosis or recent travel, and the child has not been playing with cats or other animals.

The physical examination is completely normal except for fever, mild rhinorrhea, honey-crusted lesions on the nares and upper lip, and a 4- × 5-cm, right submandibular neck mass that is erythematous, warm, and tender to palpation.

Questions

1. What are the common causes of neck masses in children?
2. What steps are involved in the evaluation of the child with a neck mass?
3. What clinical findings suggest that neck masses are neoplasms? When should neck masses be biopsied or removed?
4. What is involved in the treatment of the different types of neck masses in children?
5. When should the child with a neck mass be referred for further consultation?

A *neck mass* is any swelling or enlargement of the structures in the area between the inferior mandible and the clavicle. Normal variants, such as the angle of the mandible or tip of the mastoid bone, may occasionally appear as swellings, and the parent or guardian sometimes confuses these with neck masses. If the swelling is not a normal structure, a well-directed history and physical examination usually determine the etiology.

Lymphadenopathy from viral or bacterial throat infections is the most common cause of neck masses in children. Therefore, neck masses are common because children frequently have sore throats. Most parents and guardians know about swollen lymph glands, and they usually do not seek medical advice unless the glands become quite large or do not recede in a few days. Neck masses in children may have many other causes besides lymphadenopathy. Most of these masses may be categorized as inflammatory, neoplastic, traumatic, or congenital in origin. A well-described mnemonic in the adult literature, KITTENS (congenital/developmental anomalies, infectious/inflammatory, trauma, toxic, endocrine, neoplasms, systemic disease), can summate many of the causes of neck masses in children as well (Box 94.1).

Epidemiology

Most neck masses are benign. Almost 50% of all children 2 years of age and up to 90% of children between 4 and 8 years of age have palpable cervical lymph nodes. Although more than 25% of malignant tumors in children are found in the head and neck region (this is the primary site in only 5%), less than 2% of suspicious head and neck masses are malignant.

The epidemiology of neck masses of infectious origin depends on the infectious agent itself, geographic location of the child, and the child's immediate environment. Neck masses of viral origin may be related to focal infection of the oropharynx or respiratory tract but often are associated with generalized adenopathy. Neck masses of bacterial origin typically occur from normal bacterial flora of the nose, mouth, pharynx, and skin that secondarily spreads to lymph nodes. These organisms are not usually transmitted from person to person. Pathologic flora, such as group A streptococcus and *Mycobacterium tuberculosis*, that result in neck masses can spread by human-to-human contact, however. Additionally, cat-scratch disease is caused by *Bartonella henselae,* a vector-borne pathogen.

Clinical Presentation

Children with neck masses present in a variety of ways depending on the etiology of the mass. Typically, a swelling or enlargement in the neck, which a parent or guardian often notices more than the child, is evident. Associated signs and symptoms include fever, upper respiratory tract infection, sore throat, ear pain, pain or tenderness over the mass, changes in skin color over the mass, skin lesions of the head or neck, and dental caries or infections (Box 94.2). Malignant tumors are usually slow-growing, firm, fixed, nontender masses. Congenital neck masses and benign tumors, which have frequently been present since birth or early infancy, are soft, smooth, and cyst-like and may be recurrent. Neck masses associated with trauma are often rapidly evolving and may result in airway obstruction. Temporal development of neck masses is a helpful predictor

Box 94.1. KITTENS Mnemonic for Neck Masses

K	**Congenital/Developmental anomalies**
	Thyroglossal duct cyst
	Branchial cleft cyst
	Dermoid cyst
	Vascular malformation
I	**Infectious/Inflammatory**
	Lymphadenitis/cervical adenopathy
	Viral adenitis (multiple causes)
	Bacterial adenitis (multiple causes)
	Retropharyngeal/parapharyngeal abscesses
T	**Trauma**
	Hematoma
	Pseudoaneurysm
	Laryngocele
T	**Toxic**
	Thyroid toxicosis
	Medications (eg, carbamazepine)
E	**Endocrine**
	Thyroid neoplasms
	Parathyroid neoplasms
	Thyroiditis
	Goiter
N	**Neoplasms**
	Hemangioma
	Lipoma
	Salivary gland
	Parapharyngeal space
	Lymphoma
S	**Systemic disease**
	Sarcoidosis
	Sjögren syndrome
	Kimura disease
	Histiocytic necrotizing lymphadenitis (Kikuchi disease)
	Castleman disease
	Kawasaki disease
	AIDS

Box 94.2. Diagnosis of Neck Masses in the Pediatric Patient

Inflammatory/Infectious

- Swelling or enlargement in the neck
- Fever
- Sore throat, dental infection, skin infection of head or neck
- Pain or tenderness over the mass (usually)

Neoplastic

- Slowly enlarging mass
- Unilateral, discrete
- Firm or rubbery
- Fixed to tissue
- Deep within the fascia
- Nontender (usually)

Traumatic

- Rapidly enlarging mass
- Hematoma
- Acute airway obstruction

Congenital

- Enlargement in neck (usually present since birth or soon after)
- Soft, smooth, cyst-like
- Nontender (unless infected)
- Recurrent

Table 94.1. Rule of 7 for the Differential Diagnosis of Neck Masses

Mass Duration	*Likely Mass Etiology*
7 minutes	Trauma
7 days	Inflammation/infection
7 months	Neoplastic
7 years	Congenital

Adapted with permission from Skandalakis JE. Neck. In: Skandalakis LJ, Skandalakis JE, Skandalakis PN, eds. *Surgical Anatomy and Technique: A Pocket Manual*. 3rd ed. New York, NY: Springer; 2009:17–91.

of mass etiology. The "rule of 7" proposed by Skandalakis may be applied and adapted to pediatric neck masses (Table 94.1).

Pathophysiology

The pathophysiology of neck masses in children is dependent on etiology. Most neck masses are related to inflammation or infection of lymph nodes. Enlargement of lymph nodes usually results from proliferation of intrinsic lymphocytes or macrophages already present in the lymph node (eg, lymphadenopathy caused by a viral infection) or from infiltration of extrinsic cells (eg, lymphadenitis, metastatic tumor). Neck masses from trauma occur from leakage of fluid into the neck, and congenital anatomic abnormalities become apparent because of fluid collection or infection of the defect. The parotid gland may be enlarged from inflammation (eg, blocked salivary gland duct), infection (eg, mumps), or tumor (eg, pleomorphic adenoma), but the swelling primarily involves the face rather than the neck and obscures the angle of the jaw. Other salivary glands may be infected or obstructed and may cause submandibular swelling, erythema, and tenderness.

Differential Diagnosis

Neck masses in children are usually the result of inflammation or infection of lymph nodes, tumors of lymph nodes and other neck structures, trauma, and congenital lesions. The location of the mass is often a clue to its etiology (Figure 94.1).

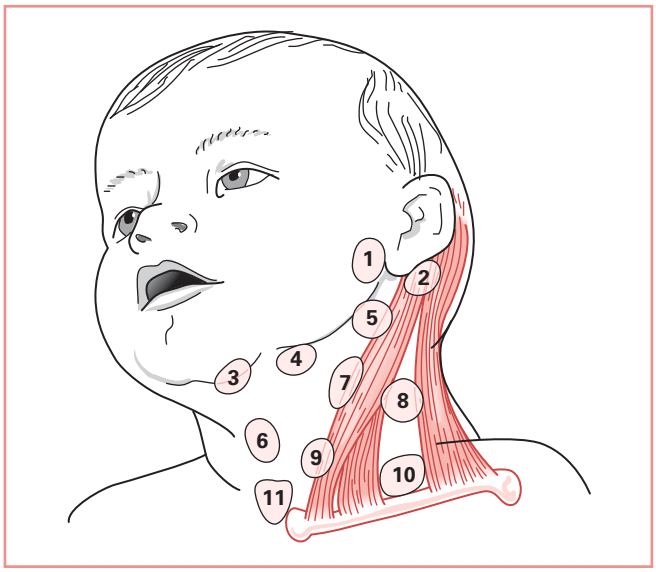

Figure 94.1. Differential diagnosis of neck mass by location. 1, Parotid—cystic hygroma, hemangioma, lymphadenitis, parotitis, Sjögren syndrome, infantile cortical hyperostosis (Caffey-Silverman syndrome), lymphoma. 2, Postauricular—lymphadenitis, branchial cleft cyst (first), squamous epithelial cyst. 3, Submental—lymphadenitis, cystic hygroma, thyroglossal duct cyst, dermoid, sialadenitis. 4, Submandibular—lymphadenitis, cystic hygroma, sialadenitis, tumor, cystic fibrosis. 5, Jugulodigastric—lymphadenitis, squamous epithelial cyst, branchial cleft cyst (first), parotid tumor, normal-transverse process C2, styloid process. 6, Midline neck—lymphadenitis, thyroglossal duct cyst, dermoid, laryngocele, normal hyoid, thyroid. 7, Sternomastoid (anterior)—lymphadenitis, branchial cleft cyst (second, third) pilomatricoma, rare tumors. 8, Spinal accessory—lymphadenitis, lymphoma, metastasis from nasopharynx. 9, Paratracheal—thyroid, parathyroid, esophageal diverticulum. 10, Supraclavicular—cystic hygroma, lipoma, lymphoma, metastasis, normal fat pad, pneumatocele of upper lobe. 11, Suprasternal—thyroid, lipoma, dermoid, thymus, mediastinal mass. Adapted with permission from May M. Neck masses in children: diagnosis and treatment. *Pediatr Ann.* 1976;5[8]:517–535, with permission from SLACK Inc.

Lymphadenopathy/Lymphadenitis

Lymphadenopathy is lymph node enlargement or hyperplasia secondary to localized infection or antigenic stimulation proximal to the involved node or nodes. Because lymphoid tissue steadily increases until puberty, palpable lymph nodes, including those in the cervical area, are a common, normal finding in children. Palpable cervical lymph nodes are present in up to 90% of children between 4 and 8 years of age. Any lymph node in the neck larger than 10 mm qualifies as cervical lymphadenopathy.

The most common cause of bilateral cervical lymphadenopathy is a viral infection of the upper respiratory tract. Lymphadenopathy usually begins and resolves with the acute infection. Occasionally, the swelling remains for several days or months, however, and a child presents because of parental or guardian concern. Bacterial pharyngitis, usually from infection with group A β-hemolytic streptococcus, is often associated with cervical lymphadenopathy. Cervical as well as generalized lymphadenopathy may occur in the child with systemic illness (eg, Kawasaki disease, sarcoid, HIV, mononucleosis). Cat-scratch disease, toxoplasmosis, fungal infection, and mycobacterial and atypical mycobacterial infections may be associated with lymphadenopathy that may later progress to lymphadenitis. Viral illnesses, including Epstein-Barr virus (ie, mononucleosis); adenovirus; enterovirus; human herpesvirus, 1, 2, and 6; and cytomegalovirus commonly cause lymphadenopathy and lymphadenitis.

Lymphadenitis is infection or inflammation of the lymph node that occurs when microorganisms and neutrophils infiltrate the node, resulting in necrosis and abscess formation. This condition usually is associated with proximal bacterial infection that drains to the affected nodes by connecting afferent lymphatic channels. Lymphadenitis often is a progression of disease, resulting in enlarged nodes that measure 2 to 6 cm. These nodes, which are typical of bacterial disease, are often termed "hot nodes," and they are erythematous, warm, tender, and sometimes fluctuant. Subacute or chronic inflammation of lymph nodes typical in illnesses such as cat-scratch disease, mycobacterial infection, or toxoplasmosis are not warm to the touch and are usually not as tender. They are typically not suppurative and may be difficult to distinguish from nodes that are simply enlarged (Figure 94.2).

Staphylococcus aureus and group A β-hemolytic streptococcus are responsible for 50% to 90% of cases of acute unilateral cervical lymphadenitis. These organisms spread from a primary site to the lymph nodes, draining those sites. Common primary sites of infection are the throat, teeth and gums, and skin (lesions), particularly on the scalp or ears. Infections at these sites may result from trauma, such as scratches or scabs, or from primary infection, such as impetigo. Anaerobic oral flora constitute a small portion of causes for bacterial cervical adenitis, especially in older children with poor dentition. *Staphylococcus aureus* or group B streptococcus usually causes cervical lymphadenitis in neonates or very young infants. Such staphylococcal infections, which often are nosocomially spread from contact in the newborn nursery, present as discrete masses. Group B streptococcus causes the "cellulitis-adenitis" syndrome, which presents as cervical adenitis associated with a facial cellulitis. *Pseudomonas aeruginosa* is an unusual cause of cervical adenitis in newborns.

Mycobacterial disease must always be considered in children of all ages who present with cervical adenitis particularly involving posterior cervical nodes. The child with *M tuberculosis* cervical adenitis often has multiple nodes, sometimes bilateral, usually nontender, and usually not erythematous or warm. These children are typically older, commonly reside in an urban setting, have a history of tuberculosis exposure, and often have an abnormal finding or findings on chest radiography. Intradermal placement of a purified protein derivative (PPD) often produces more than 15 mm of induration in most children with typical mycobacterial infection. A reaction of 5 to 14 mm may be caused by tuberculous or nontuberculous mycobacterial infection. Atypical mycobacterial infection usually occurs in children between 1 and 6 years of age with unilateral rather than bilateral lymph node enlargement and normal findings on chest radiography.

Cat-scratch disease should be considered in children who have cats or kittens or who play with them. The infection may result

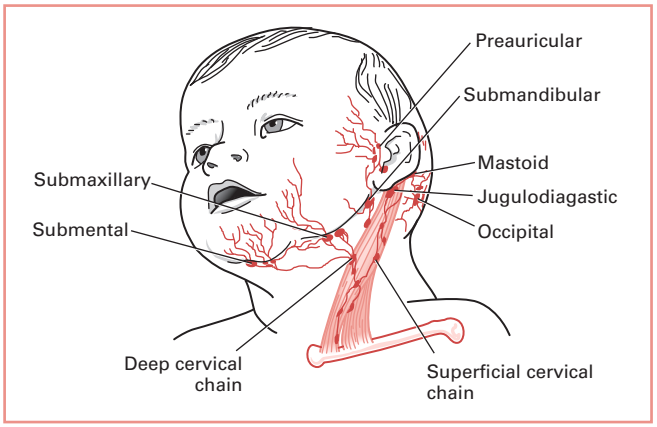

Figure 94.2. The lymphatic drainage and lymph nodes involved in infants and children with cervical lymphadenitis.
Adapted with permission from Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases.* 5th ed. Philadelphia, PA: Saunders; 2004:186.

from a cat scratch or from a cat licking a child's broken skin. If the inoculum is near the head and neck area, cervical adenitis manifests. Contact with the hand may result in axillary lymphadenitis. Occasionally, generalized lymphadenopathy is present. An associated nonpainful papule or papules where the cat scratch or lick occurred may be apparent. *Bartonella henselae* has been identified as the organism causing cat-scratch disease.

Toxoplasmosis may be accompanied by adenitis, usually in the posterior cervical area. Nodes are painless and may fluctuate in size, and children often are asymptomatic. Multiple lymph nodes are involved in approximately one-third to one-half of cases.

The child who presents with recurrent cervical adenitis and recurrent fever may have PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis). This entity usually occurs in children younger than 5 years and can be aborted with steroids.

Kikuchi disease, or histiocytic necrotizing lymphadenitis, has an Asian and female predilection and is characterized by fever, leukopenia, and cervical lymphadenopathy. The illness is self-limited, and follow-up is recommended because of a possible association with systemic lupus erythematosus.

Less common bacterial, viral, and fungal causes of cervical adenitis are listed in Box 94.3.

Tumors

Compared with other neck masses, malignant neck tumors occur rarely; nevertheless, they should be considered in any child with an enlarging or persistent neck mass. Hodgkin disease and non-Hodgkin lymphoma are the most frequent cause of head and neck malignancies in children, accounting for almost 60% of cases. Rhabdomyosarcoma is the next most frequent head and neck malignancy, followed by thyroid tumor, neuroblastoma, and nasopharyngeal carcinoma. Age is an important factor in determining the likelihood of specific tumors. Neuroblastoma, leukemia, and rhabdomyosarcoma are the most common tumor types in children younger than 6 years. Non-Hodgkin lymphoma typically occurs in preadolescence, and Hodgkin disease and thyroid carcinoma are the most common malignancies in adolescents.

Benign neck tumors, with the exception of those mentioned later in the discussion of congenital lesions, are uncommon. They include epidermoid inclusion cysts, lipomas, fibromas, neurofibromas, pilomatricomas (ie, benign skin neoplasms of hair follicle origin), keloids, goiters, and ranulas (ie, intraoral mucocele) and plunging ranula (ie, an extension of the oral ranula into the neck).

Trauma

Trauma to the neck may be associated with bleeding and edema. Large hematomas that affect vital structures are potentially life-threatening. Significant trauma and structural injury usually accompany expanding neck hematomas. Neurologic deficits and stroke after neck trauma should alert the physician to consider cervical arterial dissection. In the child with mild injury and neck hematoma, bleeding disorders are a possible cause of the hematoma. Twisting injury to the neck may result in muscle spasm of the sternocleidomastoid muscle (ie, torticollis) and an apparent mass that is the contracted muscle. Additionally, intramuscular hematoma or bleeding from vaginal delivery may cause torticollis in the neonatal period. The neck is bent toward the side of the affected sternocleidomastoid muscle. Child abuse should also be considered in children who have neck injuries that are not consistent with their histories.

Atlantoaxial rotary subluxation may result in a torticollis-like syndrome in the patient with minimal to no trauma. Because of the relatively flat nature of the facets, rotation and subluxation of C1 on C2 can occur. The patient generally presents with unilateral neck pain and inability to turn the head. The head is tilted to 1 side with the chin rotated the opposite direction from the subluxation.

A foreign body in the neck may present as a mass because of the foreign body itself (eg, piece of glass or metal, bullet) or surrounding inflammation. A crepitant neck mass following trauma to the neck or chest is suggestive of subcutaneous emphysema from tracheal injury or a pneumomediastinum. Crepitant neck masses may also occur secondary to pneumomediastinum in the child with obstructive lung disease, such as asthma or cystic fibrosis.

Congenital Lesions

The child with a congenital neck lesion can present with a neck mass in early infancy or later in childhood. Some congenital lesions are not discovered until adulthood. The most common of these benign lesions are thyroglossal duct cysts, branchial cleft cysts, lymphatic malformations (ie, cystic hygromas/lymphangiomas), and hemangiomas (Figure 94.3).

Thyroglossal duct cysts are almost always midline in the neck and inferior to the hyoid bone. They usually move upward with tongue protrusion or swallowing. Most branchial cleft cysts occur anterior to the middle third of the sternocleidomastoid muscle. Less commonly, branchial cleft cysts may appear in the posterior triangle of the neck and the preauricular area. Branchial cleft sinus tracts appear as slit-like openings anterior to the

Box 94.3. Differential Diagnosis of Neck Masses

Cervical Lymphadenopathy/Lymphadenitis

Bacterial Origin

- *Staphylococcus aureus* (methicillin sensitive)
- *Staphylococcus aureus* (methicillin resistant)
- Group A β-hemolytic streptococcus
- *Mycobacterium tuberculosis*
- Atypical mycobacteria
- Cat-scratch disease (*Bartonella henselae*)
- Anaerobes
- Gram-negative enteric bacteria
- *Haemophilus influenzae*
- Plague
- Actinomycosis
- Diphtheria
- Tularemia
- Brucellosis
- Syphilis
- Group B streptococcus (neonates)

Viral Origin

- Epstein-Barr virus (infectious mononucleosis)
- Adenovirus
- Cytomegalovirus
- Human herpesvirus types 1 and 2
- Enterovirus
- HIV
- Measles
- Rubella
- Human herpesvirus 6
- Influenza virus

Fungal Origin

- Histoplasmosis
- Coccidioidomycosis
- Aspergillosis
- Candidiasis
- Sporotrichosis
- Cryptococcosis

Parasitic Origin

- Toxoplasmosis
- Leishmaniasis

Tumor

Malignant

- Hodgkin disease
- Non-Hodgkin lymphoma
- Lymphosarcoma
- Rhabdomyosarcoma
- Neuroblastoma
- Leukemia
- Langerhans cell histiocytosis
- Thyroid tumors
- Nasopharyngeal squamous cell carcinoma
- Salivary gland carcinoma

Benign

- Epidermoid cyst
- Lipoma
- Fibroma
- Neurofibroma
- Pilomatricoma
- Keloid
- Goiter
- Osteochondroma
- Teratoma (may be malignant)
- Ranula

Congenital Disorders

Hemangioma

- Cystic hygroma (lymphangioma)
- Branchial cleft cyst
- Thyroglossal duct cyst
- Laryngocele
- Dermoid cyst
- Cervical rib
- Sternocleidomastoid tumor

Trauma

- Hematoma (acute or organized)
- Subcutaneous emphysema
- Foreign body
- Arteriovenous malformation

Immunologic Disorders

- Local hypersensitivity reaction (sting or bite)
- Pseudolymphoma (from phenytoin)
- Serum sickness
- Sarcoidosis
- Infantile cortical hyperostosis (Caffey-Silverman syndrome)
- Kawasaki disease
- Systemic lupus erythematosus
- Juvenile rheumatoid arthritis
- Kikuchi disease (necrotizing lymphadenitis)
- Kimura disease

Miscellaneous

- Sialadenitis
- Parotitis
- Storage disorders
- Niemann-Pick disease
- Gaucher disease
- Obstructive airway disease (asthma, cystic fibrosis)

lower third of the sternocleidomastoid muscle and may present as neck masses if they become infected. Thyroglossal duct cysts and branchial cleft cysts may also present for the first time as infected neck masses.

Cystic hygromas are usually large, soft, easily compressible masses found in the posterior triangle behind the sternocleidomastoid muscle in the supraclavicular fossa. They transilluminate well. Two-thirds of cystic hygromas are present at birth, and 80% to 90% are identified before 3 years of age. They are more common on the left side of the neck. Cystic hygromas occasionally become secondarily infected, with findings of erythema, warmth, and tenderness.

Hemangiomas are usually not present at birth but appear in early infancy and may enlarge rapidly. In most cases, they recede spontaneously by 9 years of age. They are usually much smaller than cystic hygromas, do not transilluminate, and may be recognized by their reddish color (eg, capillary or strawberry hemangioma) or by a bluish hue of the overlying skin (eg, cavernous hemangioma).

The small infant who presents with torticollis should be examined for a sternocleidomastoid mass ("tumor"), which represents fibrosis and contracture of that sternocleidomastoid muscle so that the head tilts toward the affected side with the chin rotating to the opposite side. Contusion of the sternocleidomastoid muscle from traumatic extraction of the head during delivery with subsequent hemorrhage and healing has been implicated as the cause of the fibrotic mass. It is more likely, however, that this mass occurs before birth, because it contains mature fibrous tissue. Additionally, the mass may be present following cesarean section and is associated with hip dysplasia and other congenital lesions, which suggests that the condition is related to abnormal positioning in utero. Venous occlusion of the sternocleidomastoid muscle in utero or at the time of delivery has also been proposed as a cause.

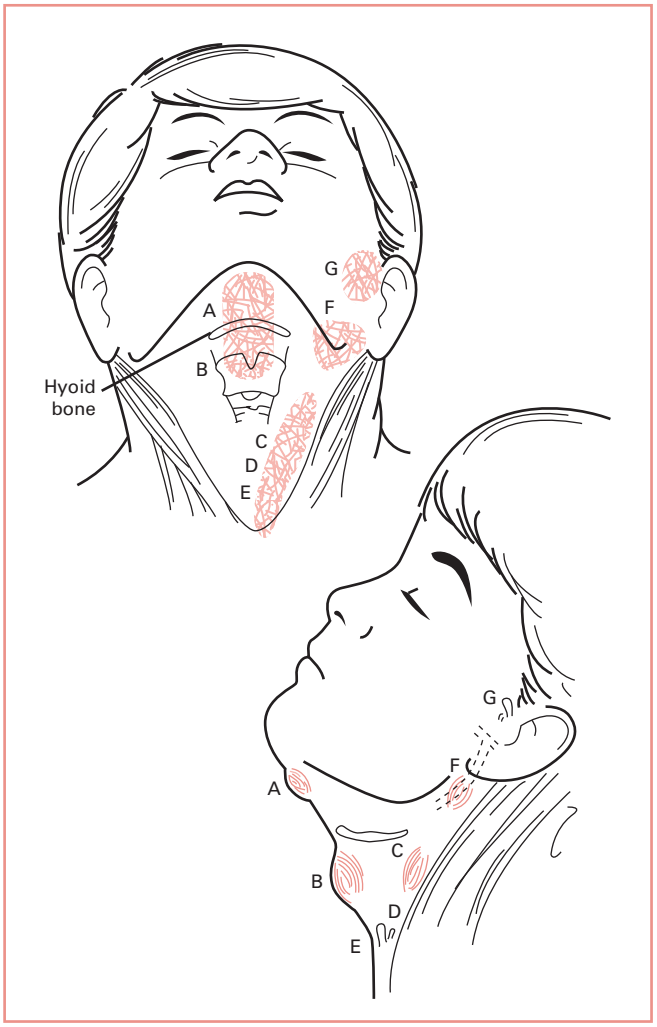

Figure 94.3. Frontal (upper left) and lateral (lower right) views of head and neck congenital lesions that occur in children. The shaded areas denote the distribution in which a given lesion may be found. A, Dermoid cyst. B, Thyroglossal duct cyst. C, Second branchial cleft appendage. D, Second branchial cleft sinus. E, Second branchial cleft cyst. F, First branchial pouch defect. G, Preauricular sinus or appendage.

Reproduced with permission from Fleisher GR, Ludwig S, Henretig FM, eds. *Textbook of Pediatric Emergency Medicine.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:1594.

Evaluation

History

A thorough history is important in establishing the etiology of the neck mass (Box 94.4).

Physical Examination

A general physical examination should be performed. The neck mass should be examined for anatomic location, color, size, shape, consistency, tenderness, fluctuation, and mobility. The mass should also be measured. A mass that has an audible bruit or palpable thrill is suggestive of a vascular malformation or traumatic injury. The airway should be assessed for patency, including presence of stridor, trismus, drooling, or other signs of airway compromise. The head, neck, and face should be examined for lesions, most often infections that drain into neck lymph nodes. Lesions can frequently be found on the scalp, neck, face, ears, mouth, teeth, tongue, gums, and throat. Hairstyles, such as tight braids, can sometimes provide ports of entry for bacteria. Occasionally, sinus tracts or fistulas may be the entry point of infection. Additionally, other lymph node groups should be examined to determine if the lymphadenopathy is local or generalized. Particular attention should be paid to the supraclavicular area because enlarged supraclavicular nodes are more frequently associated with malignant pathology, such as Hodgkin disease. The chest should be examined for use of accessory muscles, equality of breath sounds, and wheezing. The abdomen should be examined for hepatosplenomegaly.

Laboratory Tests

Laboratory tests are rarely indicated in the child with cervical lymphadenopathy or lymphadenitis of acute onset. Although a rapid antigen detection test or throat culture for group A streptococci is helpful in the child with suspected streptococcal sore throat, it may be unnecessary if antibiotic therapy is empirically prescribed for lymphadenitis. If the adenitis is fluctuant, aspiration and culture may be helpful in determining the specific bacteriologic diagnosis.

Box 94.4. What to Ask

Neck Masses

- How old is the child?
- How long has the neck mass been present?
- What signs and symptoms are associated with the neck mass?
- Has the child been exposed to tuberculosis?
- Has the child consumed any unpasteurized cow's milk?
- Has the child been in contact with any cats or kittens? Rabbits? Other animals?
- Has the child traveled to areas where endemic diseases, such as histoplasmosis or coccidioidomycosis, are prevalent?
- Has the child suffered any trauma recently?
- Does the child have any allergies?
- Does the child have any risk factors for HIV?

Fine-needle aspiration cytology and polymerase chain reaction assays may help differentiate between tuberculous and nontuberculous mycobacterial disease. Superficial cervical nodes or axillary nodes, if enlarged, are appropriate first-line aspiration sites because of their superficial nature. A PPD test should be applied to all children who present with lymphadenitis.

If the adenitis does not resolve or improve after 2 to 3 days of observation or therapy, laboratory tests directed by the history and physical examination should be considered. A complete blood cell count with differential and a monospot test or serologic antibody tests for Epstein-Barr virus may be helpful in the diagnosis of infectious mononucleosis. If the neck mass is a hematoma and a bleeding disorder is suspected, a complete blood count with platelet count, prothrombin time, and partial thromboplastin time should be obtained. Possible additional tests include an erythrocyte sedimentation rate and C-reactive protein. If indicated, serologic tests for toxoplasmosis, cytomegalovirus, human herpesvirus 6, coccidioidomycosis, histoplasmosis, tularemia, *B henselae,* and syphilis should be performed. Skin tests for fungi should be considered in those patients coming from endemic areas. These tests should be placed after serologic tests are performed to avoid false-positive results on serologic testing.

Similar laboratory tests should be considered for the child who presents for the first time with enlarged or enlarging lymph nodes of long duration or who does not respond after 2 weeks of antibiotic therapy. The physician may choose to do more of these laboratory tests at the initial evaluation or after a therapeutic trial because the likelihood of viral lymphadenopathy decreases and the possibility of a more unusual etiology increases. HIV testing should also be considered.

Thyroid function testing should be considered in the child with a thyroid mass or suspected thyroglossal duct cyst. Ultrasonography or thyroid scan should be considered for the child with a thyroid mass.

Unless cat-scratch disease is very likely, urgent lymph node biopsy is indicated for enlarged supraclavicular nodes or lymph nodes in the lower half of the neck, rapidly progressive and enlarging nodes, fixed nodes, nodes deep within the fascia, or firm or hard nodes. The child with a persistent fever or weight loss should undergo a biopsy at 1 week if a diagnosis has not been established. The asymptomatic child without an established diagnosis should undergo a biopsy at 2 weeks if the node increases in size, at 4 to 6 weeks if the node is not increased in size but is persistent, and at 8 to 12 weeks if the node has not regressed to a normal size. In some cases, the initial biopsy is nondiagnostic, but on subsequent biopsy, a specific diagnosis may be made. Consequently, the child with persistent adenopathy should be followed closely and undergo biopsy again if indicated. Fine-needle aspiration biopsy in children is controversial but has some demonstrated benefits. It is increasingly being used to differentiate between benign and malignant disease and to potentially decrease the need for open biopsy. If malignancy is a consideration, however, consultation with an oncologist is advisable to determine the biopsy method of choice.

Imaging Studies

A chest radiograph should be obtained in all children with suspected tuberculosis or tumor (eg, enlarged supraclavicular nodes) as well as in children with crepitant neck masses or in whom the diagnosis of the adenitis remains uncertain. If a foreign body in the neck is suspected, anteroposterior and lateral neck radiographs should be obtained.

Almost all neck masses can be evaluated by ultrasonography, computed tomography (CT), or magnetic resonance (MR) imaging. Because there is no ionizing radiation associated with ultrasonography and because it is quickly available, is noninvasive, and does not need sedation, it is the initial imaging study of choice, particularly for thyroid masses, thyroglossal duct cysts, branchial cleft cysts, and parotid masses. Ultrasonography is a reasonable screening tool for all superficial neck masses. If malignancy is suspected or the mass cannot be delineated in the field of view, MR imaging or CT may be more definitive studies. Color Doppler ultrasonography is helpful in differentiating cystic from solid masses and determining if the mass is vascular. Additionally, demonstration of a normal thyroid gland by ultrasonography in the patient with a thyroglossal duct cyst confirms a source of thyroid hormone. Consequently, a thyroid scan is not necessary.

Computed tomography and MR imaging provide better definition and extent of the mass than ultrasonography. Computed tomography with contrast is the preferred method of imaging for deep neck abscesses that present with a neck mass and for enlarged salivary glands. Computed tomography or MR imaging is superior to plain radiography for diagnosing rotary subluxation. Magnetic resonance imaging provides the best anatomic detail, and it is the preferred imaging study for children with vascular and lymphatic malformations and neoplasms; however, it is not as available as CT and often requires a greater degree of sedation.

Management

Neck masses are rarely acutely life-threatening. If a neck mass impinges on the airway, the affected child may experience stridor, hoarseness, drooling, increased effort of breathing, unequal breath sounds, or evidence of shock. Resuscitation and stabilization should be initiated immediately. There should be a low threshold to establish a secure airway in a child with an expanding traumatic neck mass. The algorithm in Figure 94.4 outlines the management of cervical lymphadenitis.

The child with lymphadenitis who does not appear toxic and has no evidence of sepsis may be treated empirically with oral antibiotics that cover *S aureus,* particularly methicillin-resistant *S aureus* (MRSA), and group A β-hemolytic streptococcus. Clindamycin or a combination of cephalexin (administered until the culture from the lymph node, if available, for group A streptococcus is negative) and trimethoprim-sulfamethoxazole may be used to provide coverage for these organisms. If methicillin-susceptible *S aureus* is cultured and sensitivities are determined, a first-generation cephalosporin, such as cephalexin (50 mg/kg per day), dicloxacillin (50 mg/kg per day), or amoxicillin-clavulanate potassium (40 mg/kg per day based on the amoxicillin component)

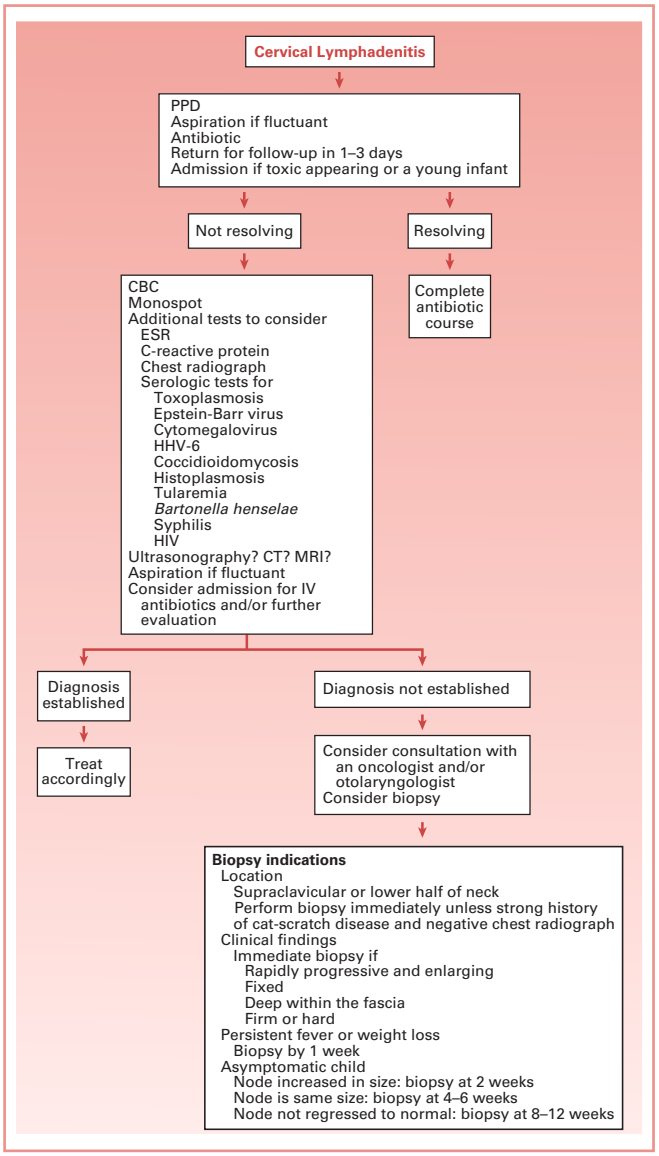

Figure 94.4. Management of cervical lymphadenitis.

Abbreviations: CBC, complete blood cell count; CT, computed tomography; ESR, erythrocyte sedimentation rate; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus; IV, intravenous; MRI, magnetic resonance imaging; PPD, purified protein derivative.

may provide satisfactory coverage. Treatment should be continued for at least 10 days but for no less than 5 days after resolution of acute signs and symptoms. Lack of clinical improvement after 36 to 48 hours suggests that the diagnosis and proposed therapy need to be reevaluated.

Infants and younger children, as well as those older children who do not respond to oral antibiotic therapy, may require admission for intravenous antibiotics, such as clindamycin or vancomycin (especially for a potentially life-threatening infection) until culture and sensitivity results are available. If methicillin-susceptible *S aureus* is cultured and sensitivities are determined, oxacillin or a cephalosporin may be satisfactory alternatives. Incision and drainage of large, fluctuant nodes that are clearly from bacterial disease should be done in consultation with an otolaryngologist or surgeon to promote resolution of the lymphadenitis. Alternatively, treatment by needle aspiration instead of incision and drainage has been advocated by some physicians. If *M tuberculosis,* atypical mycobacterial infection, or infection with *B henselae* is suspected, incision and drainage should not be done because persistent sinus tracts may result.

Atypical mycobacterial infection is generally unresponsive to treatment with antituberculous medications. Surgical excision of all visibly affected nodes, deep as well as superficial, is recommended. In cases in which surgery is refused or is incomplete or disease is recurrent, however, macrolide or azalide monotherapy (clarithromycin or azithromycin) or a macrolide in combination with ethambutol hydrochloride, rifampin, or rifabutin has been helpful in managing nontuberculous adenitis. Tuberculous mycobacterial adenitis usually responds to short-course medical therapy. Antituberculous medication for 6 to 9 months is recommended.

Lymphadenitis from cat-scratch disease usually resolves spontaneously in 2 to 4 months. Azithromycin may shorten the course and is recommended by some experts. Antibiotic therapy is indicated if a child is severely ill or appears toxic with systemic cat-scratch disease, has hepatic or splenic involvement, is immunocompromised, develops meningoencephalitis, or is admitted for a suppurative adenitis. Treatment with oral antibiotics, such as azithromycin, rifampin, trimethoprim-sulfamethoxazole, or ciprofloxacin, may be beneficial. If no improvement occurs, the addition of parenteral gentamicin to the regimen may be considered. Aspiration is indicated to relieve symptoms in the patient with fluctuant or painful suppurative nodes. Incision and drainage should not be done. Total removal of the node is sometimes necessary to effect a cure.

No specific therapy exists for lymphadenitis caused by *Toxoplasma gondii*. Excision of the affected node may be indicated if the diagnosis is questionable.

If a tumor is suspected, consultation with a pediatric oncologist is recommended. The mass should be biopsied for a definitive diagnosis. If it is malignant, a treatment plan should be generated with the appropriate consultants.

Congenital torticollis from fibrosis of the sternocleidomastoid muscle is best managed nonsurgically. Repetitive passive range-of-motion exercises over several weeks usually result in loosening the tight muscle and increasing the range of motion. Rotary subluxation is generally treated conservatively with immobilization because most cases resolve. More severe cases are treated in traction by a neurosurgeon.

Fifty percent of hemangiomas will usually resolve by the time children are 5 years of age, 70% by age 7, and 90% by age 9. Propranolol may expedite evolution of hemangioma. Surgical intervention is rarely indicated. Recent literature has demonstrated a profound benefit with oral propranolol therapy in the management of hemangioma. Oral propranolol therapy demonstrates a considerable flattening and effacement of cutaneous and mucous membrane hemangiomas within 24 hours and marked improvement after weeks of propranolol therapy. Multiple studies suggest

excellent efficacy with oral propranolol for the management of life-threatening, vital-organ–impairing (eg, vision loss), refractory, or disfiguring hemangioma. Dosing is titrated up to 3 mg/kg per day and continued for up to 6 months until resolution of the hemangioma. The patient should be closely monitored for hypoglycemia, bradycardia, hypotension, and congestive heart failure during institution of therapy. Propranolol initiation is increasingly performed in the outpatient setting, and evidence exists indicating that initiation can be safely performed in the healthy child. Atenolol appears to work just as well as propranolol, but most studies are performed with propranolol. Corticosteroids, previously the mainline treatment modality for hemangiomas, are now considered an adjunctive treatment with propranolol. Additional therapies include interferon-α-2a and various cytotoxic medications. Interferon-α-2a has been associated with transient or permanent neurologic disabilities, so it is important to balance the benefits and risks of this medication. High-potency topical corticosteroids (eg, clobetasol propionate) or topical beta blockers (eg, timolol) may be used in selected cases.

Surgical excision is usually indicated for cystic hygroma (ie, lymphangioma), branchial cleft cyst, and thyroglossal duct cyst. Thyroid ultrasonography should be performed before removal of a thyroglossal duct cyst to determine the presence of ectopic thyroid tissue. Endocrinologic consultation is recommended in these cases. Thyroid nodules in children may be cancerous, especially in children who have undergone irradiation to the head and neck region. Consultation with an endocrinologist and surgeon should be obtained. Goiters in children should be evaluated by an endocrinologist.

Prognosis

The prognosis for children with neck masses is generally excellent but differs depending on the cause. Children with an infectious etiology do quite well if diagnosed and treated with appropriate antimicrobial agents. Mycobacterial lymphadenitis may result in sinus tract formation or disseminated disease. Surgical excision usually cures atypical mycobacterial infection. Cat-scratch disease is usually benign and self-limited. Encephalopathy is a rare complication of this disorder.

The prognosis for benign tumors of the neck is excellent. The outlook for the child with a malignant neck tumor depends on etiology of the tumor and spread of the malignancy to other organs. Early diagnosis and treatment are important in improving outcome.

The child with a neck mass resulting from trauma usually has sustained significant injury. The outcome often depends on establishment of an airway, provision of ventilatory support, and management of hemodynamic instability. Availability of surgical support is often essential to a good outcome.

The child with a congenital lesion of the neck usually has an excellent prognosis. Some lesions resolve spontaneously, whereas others require simple surgical excision. Cystic hygromas may require multiple operations for complete removal because of their diffuse nature.

CASE RESOLUTION

The boy has signs and symptoms consistent with submandibular bacterial cervical lymphadenitis. The location of the neck mass in relation to the honey-crusted lesions (nonbullous impetigo) implicates spread of bacteria from the primary site of infection to the lymph nodes. Laboratory tests are unnecessary because the child does not appear septic. Culture of the impetigo may be helpful in determining if the organism causing the infection is MRSA. If the affected lymph node is fluctuant, aspiration of fluid for culture is indicated and incision and drainage should be considered. The child should be treated as an outpatient with an oral antibiotic directed against MRSA and group A β-hemolytic streptococcus, such as clindamycin or a combination of cephalexin and trimethoprim-sulfamethoxazole, as well as an analgesic for pain as necessary. If methicillin-susceptible *S aureus* is cultured and sensitivities are determined, cephalexin, amoxicillin-clavulanic acid, or dicloxacillin may be administered. If the child appears toxic or if marked lymph node enlargement is present, the child should be admitted for intravenous antibiotics. A PPD skin test should be placed for tuberculosis. The child should be followed up in 1 to 3 days for clinical improvement depending on the severity of the infection.

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CHAPTER 95

Allergic Disease

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CASE STUDY

A 3-year-old girl is rushed to an urgent care center by her mother after the girl developed a pruritic rash, facial swelling, and hoarseness shortly after eating a peanut butter sandwich. She had eaten peanut butter once before, and her parents noticed a few small hives on her cheek that self-resolved. Previously, the girl has been well except for recurrent nasal congestion every spring that has responded to antihistamines. She has also had an intermittent skin rash that has been managed with topical steroid creams. She has never before had an acute reaction and has no history of asthma. Her father had asthma as a child.

Physical examination reveals a well-developed, 3-year-old girl with marked facial swelling and a generalized rash who is in mild respiratory distress. Vital signs, including blood pressure, are normal. The girl has a diffuse, blotchy, erythematous rash with central wheals; a hoarse voice; and a mild expiratory wheeze on auscultation of her chest. The remainder of the examination is normal.

Questions

1. What are the various symptoms of allergic disease?
2. What is the appropriate evaluation of a child with manifestations of allergic disease?
3. What allergens are common triggers for allergic symptoms?
4. What treatment is helpful for the child with manifestations of allergic disease?
5. Can allergic disease be prevented?

Allergic disease occurs frequently in the general population and manifests in many ways. Types of allergic disease include asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, urticaria, angioedema, anaphylaxis, and food, insect, and drug allergies. Allergic symptoms result from the production of specific immunoglobulin (Ig) E antibody after exposure to a foreign antigen. The process has 2 steps. The first step is the sensitization or antibody induction stage. The individual develops IgE antibody against an inhaled, ingested, or injected substance. The process usually takes from several days to weeks for medications and foods to months to years for inhalant allergens, such as pollens. Newly formed antigen-specific IgE antibody adheres to IgE receptors on circulating blood basophils or to tissue mast cells. On reexposure, the allergen binds to several specific IgE antibodies on the surface of these cells and triggers degranulation of preformed and rapidly formed mediators, such as histamine and leukotrienes, resulting in the early phase of the reaction. Clinically, this is manifested by sneezing, rhinorrhea, and pruritus in allergic rhinitis; wheal and/or flare in urticaria or angioedema; and shock in anaphylaxis. Mast cell degranulation also releases peptides that attract inflammatory peptides, such as interleukin-4 and interleukin-5, which release mediators that result in chronic inflammation. This late phase of inflammation is responsible for congestion and hyperreactive mucosa in allergic rhinitis and delayed reactions in anaphylaxis. The remaining manifestations of allergies, including allergic rhinitis, conjunctivitis, food allergies, and anaphylaxis are the focus of this chapter.

Epidemiology

Allergic disease or some form of allergic symptoms occur in 12% to 20% of the general population in the United States. The prevalence of symptoms varies depending on the population being investigated. Factors such as age, genetic background, and place of residence are significant. Allergic rhinitis occurs in 10% of children, as does asthma. Up to 6% of children younger than 3 years develop food allergies. Urticaria occurs at some time in approximately 10% to 20% of the population.

It is generally accepted that if neither parent is atopic (ie, has the allergic tendency to manufacture IgE on antigen exposure), the chance that a child of theirs will develop allergic symptoms is less than 1 in 5. If 1 parent is atopic, however, the risk doubles. If both parents are atopic, the chance of their child developing allergic symptoms is better than 3 in 5.

Clinical Presentation

Children with allergic disease frequently present with persistent, clear rhinorrhea; sneezing; postnasal drip; or injected pruritic conjunctivitis. Skin manifestations include dry, scaling, erythematous rashes; wheals; and subcutaneous swelling (Box 95.1). A recurrent cough or wheezing on chest examination is further evidence of allergic disease.

Pathophysiology

Allergic rhinitis, like all allergic manifestations, is caused primarily by an antigen-antibody reaction involving IgE. Antigen-specific

Box 95.1. Diagnosis of Allergic Disease in the Pediatric Patient

- Chronic, clear rhinorrhea
- Nasal congestion
- Conjunctival tearing and pruritus
- Conjunctival injection
- Wheezing
- Chronic cough
- Postnasal drip
- Mouth breathing
- Snoring
- Skin findings of atopic dermatitis or urticaria
- Seasonal variability of symptoms
- Occurrence of symptoms after exposure to an antigen
- Family history of allergic disease
- Acute onset of symptoms following exposure to possible allergen

IgE is produced by the B lymphocytes of allergic patients on exposure to a particular antigen, which attaches to immune cell receptors located on basophils in the circulation and mast cells in the tissue. On reexposure, the antigen reacts with this specific IgE on the mast cells, releasing vasoactive mediators, including histamine, leukotrienes, kinins, and prostaglandins. These mediators produce vasodilation and edema, and they also stimulate neural reflexes to produce mucous hypersecretion and sneezing. Eosinophils, basophils, and other inflammatory cells induced by chemotactic factors enter the affected organ, releasing mediators and thereby worsening the inflammation and damaging tissues. Secretions and released tissue proteins exacerbate existing edema. Other immunologic mechanisms can also be involved.

Children with allergic rhinitis often present with rhinorrhea, sneezing, nasal pruritus, and congestion. Allergic eye symptoms (ie, allergic rhinitis, conjunctivitis) may accompany nasal rhinitis with ocular pruritus, injection of the conjunctiva, and clear tearing. Younger children may present with repeated sniffing, snorting, coughing, or scratching an itchy palate with their tongue (ie, palatal clicking) because they usually cannot blow their nose.

Urticaria, the clinical rash produced by capillary leak vasodilation and edema of the skin, occurs when histamine and other vasoactive peptides, such as prostaglandins and leukotrienes, are released from the epidermal mast cells. Basophils have been identified in biopsies of these lesions. Mast cell degranulation occurs commonly in sensitized patients on reexposure to antigens found in food, medications, supplements, and insect venom when antigen-specific IgE found on mast cells is triggered by these allergens. The mast cell, however, can also be activated and release mediators by a wide number of stimuli independent of IgE mechanisms, including viral, bacterial, parasitic, and fungal infections; collagen vascular disease; malignancy; and endocrine disease. Some patients also experience urticaria to physical factors, such as heat, cold, pressure, sun, and vibration.

An urticarial rash appears as erythematous lesions of various sizes with pale, papular centers that typically are not painful unless traumatized by scratching. Lesions may coalesce, the rash blanches on pressure, and the skin is intact. Usually, individual lesions last less than 24 hours at a single location, although they often recur in the same area.

Angioedema is the extension of the urticarial process deeper into the dermis of the skin, producing swelling. The mucous membranes may be affected. Pathophysiology is similar to that of urticaria. A hereditary type of angioedema, which is not allergy related, is caused by an inherited deficiency of the C1 esterase inhibitor, resulting in unopposed production of the potent vasoactive amine bradykinin. Unlike urticaria, no distinct rash exists and the skin is not pruritic. Capillary leak and edema of the dermis results in tissue swelling, a sense of tightness, and sometimes pain. Involvement of the abdominal viscera may result in colicky abdominal pain.

Chronic urticaria and angioedema is that which persists beyond 6 weeks. More than 90% of chronic urticaria and angioedema in an otherwise healthy patient is idiopathic and is termed *chronic idiopathic urticaria*. Up to one-half of patients with chronic idiopathic urticaria have the circulating mast cell anti-IgE receptor antibody IgG, which repeatedly causes degranulation of cutaneous mast cells in these patients.

Anaphylaxis is an acute, systemic allergic reaction resulting from antigen-specific IgE on mast cells and basophils. Pathophysiology is similar to that of allergic rhinitis, but the reaction occurs in mast cells in many locations simultaneously, and prior sensitization to an allergen is essential. Anaphylactic reactions may be life-threatening. Massive vasoactive mediator release results in large reductions in peripheral resistance caused by capillary leak and vasodilation. This eventually overwhelms compensatory increases in cardiac output (blood pressure = cardiac output × total peripheral resistance), resulting in hypotension and shock. Pooling of blood in the periphery also reduces venous return, resulting in diminished preload and cardiac output. Reactions can occur in seconds or as late as 1 hour after exposure. Up to 20% of adults and 15% of children may experience a late or biphasic phase (ie, a recurrence of symptoms after resolution of anaphylaxis without trigger reexposure) hours after the first reaction because of late recruitment and activation of basophils and other inflammatory cells. Children with anaphylaxis have a reduced risk for late phase reaction, likely of approximately 3% to 5%. Common causes of anaphylaxis include food, medications and biologic agents, and stinging insect venom. The drug most frequently implicated in anaphylaxis is penicillin. Patients initially experience tightness and intense itching of the skin. Nausea, vomiting, and abdominal pain may ensue, followed by the full spectrum of anaphylaxis. Certain agents, such as radiocontrast media and blood products, may cause massive mast cell degranulation via an IgE-independent mechanism, resulting in clinical symptoms that are indistinguishable from anaphylaxis; these reactions, termed *anaphylactoid reactions*, are generally less severe than anaphylaxis.

Confusion exists among less experienced clinicians as to what combination of symptoms constitutes anaphylaxis, which may result

in either overdiagnosis or underdiagnosis. Generally, anaphylaxis is highly likely in the setting of cutaneous findings plus respiratory or hemodynamic compromise; involvement of 2 or more of the following systems: skin, respiratory, and gastrointestinal (GI) organ; and hemodynamic compromise (Box 95.2).

A *food allergy* may produce IgE-mediated reactions and diseases, including acute urticaria or angioedema, anaphylaxis, acute rhinitis, and atopic dermatitis. The localization of IgE-sensitized mast cells to that specific antigen determines the symptoms produced by an allergy. The antigen enters through the GI mucosal barrier. Intact food proteins may enter the circulation, stimulating the production of antigen-specific IgE. Additionally, food allergens may result in some non–IgE-mediated diseases, including eosinophilic esophagitis, food protein-induced enterocolitis syndrome (FPIES), allergic proctocolitis, and Heiner syndrome, a rare reaction to cow's milk protein. Finally, many patients have a nonimmune-mediated reaction to foods termed *food intolerance* (eg, lactose intolerance).

In young children, the most common food allergens are milk, egg, soy, wheat, peanuts, and tree nuts, whereas adults and older children are allergic to peanuts, shellfish, and fish. Adults and older children with atopic predisposition and allergic rhinitis or asthma often become sensitized to tree and weed pollens via the respiratory tract. They exhibit cross-reactivity between common elements of these inhalant tree or weed pollen peptides and similar peptides found in fruits and vegetables, resulting in local (ie, oral) IgE symptoms of tingling and mild swelling when ingesting these foods. These mild reactions are called *pollen-food allergy syndrome*.

Patients with IgE-mediated food allergy may experience urticaria or angioedema, eczematoid dermatitis, vomiting, wheezing, and, in severe cases, anaphylaxis. Eosinophilic esophagitis presents with nonspecific symptoms, including vomiting, reflux, dyspepsia, poor appetite, and failure to thrive. Infants with FPIES present with severe vomiting and bloody stool, generalized edema, and, in some cases, shock on initial ingestion of cow's milk, although soy and other foods have, in rare cases, been implicated. Allergic proctocolitis presents in infants on first exposure to cow's milk protein, including via human milk, but symptoms are mild and involve only blood-streaked stool. *Heiner syndrome* is a rare IgG-mediated reaction to cow's milk protein that results in anemia, wheezing, hemoptysis, melena, and pulmonary infiltrates. Older patients with pollen-food allergy syndrome to fruits and vegetables experience lip, oral mucosa, and tongue tingling as well as minimal swelling. These reactions are local and mild and rarely progress to anaphylaxis.

Box 95.2. Practical Definition of Anaphylaxis

One of the following criteria is fulfilled:

1. Acute onset of mucosa or cutaneous findings, such as hives, pruritus, lip swelling, AND 1 of the following:
   - Respiratory compromise
   - Cardiovascular compromise (eg, hypotension) or end-organ dysfunction (eg, syncope)
2. TWO of the following after likely exposure to allergen:
   - Respiratory compromise
   - Mucocutaneous symptoms
   - Hypotension
   - Persistent gastrointestinal symptoms
3. Reduced blood pressure appropriate for age

Adapted from Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med.* 2006;47(4):373–380, with permission.

Differential Diagnosis

Most patients with allergic rhinitis have clearly identifiable signs and symptoms consistent with a history of exposure; other etiologies should be considered, however, especially with poor response to treatment. Children experience many upper viral respiratory infections each year that can mimic allergic rhinitis. Many types of nonallergic rhinitis exist and the mechanisms responsible are unclear, although cholinergic pathways are likely involved. Vasomotor and cholinergic rhinitis often result in copious amounts of clear rhinorrhea in response to cholinergic stimuli, such as cold air (ie, skier nose) or spicy foods (ie, gustatory rhinitis). Medications such as angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs may cause rhinitis, but this usually occurs in adults and older children. Similarly, hormone surges, such as during ovulation, may result in nasal symptoms. Overuse of topical decongestants containing α-agonists results in rebound rhinitis (ie, rhinitis medicamentosa). In children, foreign bodies produce unilateral nasal obstruction and often malodorous purulent discharge. Patients with a history of basilar skull fracture with cerebrospinal fluid leak may present with clear rhinorrhea.

Urticaria and angioedema have a distinct clinical presentation that is usually easy to distinguish from other skin conditions. As mentioned previously, numerous possible etiologies of urticaria and angioedema exist, and determining the cause of a given instance is challenging. Urticaria and angioedema may last for weeks; however, individual lesions should persist for less than 24 hours, although they can recur at 1 area. *Urticarial vasculitis* is a distinct form of urticaria that results from the persistence of antigens arising from collagen vascular disease, serum sickness, and neoplasia. The rash from urticarial vasculitis lasts for more than 24 hours, has a burning sensation, causes less pruritus than other forms of urticaria, and leaves an area of hyperpigmentation on resolution. Other rashes that mimic urticaria include insect bites, erythema multiforme, mastocytosis, and contact dermatitis. Anaphylaxis is usually associated with cutaneous, respiratory, cardiovascular, and systemic symptoms, such as skin rash, edema, wheezing, arrhythmia, occasionally fever, and shock. A history of an acute exposure to a potential allergen is more likely to be seen with anaphylaxis than with urticaria.

Signs and symptoms of food allergies vary. It is important to determine whether actual immune-mediated disease exists or if the patient has food intolerance. Food may contain toxic peptides, such as in *scombroid fish poisoning*, in which bacteria in unrefrigerated

fish convert amino acids into histamine, which results in allergy-like symptoms when ingested. Patients with enzyme deficiencies, such as lactose intolerance, experience GI symptoms when eating dairy products. Alternatively, food may have pharmacologic properties, such as those found in caffeinated drinks.

Non–IgE-mediated food allergies may produce signs and symptoms similar to other disorders that can be life-threatening, such as FPIES, which often is indistinguishable from sepsis; Heiner syndrome, which shares similarities with serious diseases (eg, pulmonary hemosiderosis); and Wegener granulomatosis. These conditions must be ruled out during the evaluation of these forms of food allergies.

Most patients with symptoms associated with foods do not have an immune-mediated reaction but have food intolerances. Some manifestations have well-defined mechanisms, such as in lactase deficiency or galactosemia, whereas others, such as gustatory rhinitis, are less clear.

Evaluation

History and Physical Examination

Allergic Rhinitis and Conjunctivitis

The child with possible allergic rhinitis has a history of sneezing, itching, nasal discharge, and nasal blockage. The eyes, ears, palate, and throat may itch. The child may also have a history of mouth breathing and snoring at night, sleep disturbances, and daytime fatigue from nasal obstruction. Other signs include sinusitis, postnasal drip, halitosis, cough, and morning sore throat. Symptoms may be seasonal or associated with a specific stimulus. Additionally, systemic symptoms of fatigue, headache, anorexia, and irritability may be present.

The history should also include a search for other manifestations of allergies (eg, wheezing, atopic dermatitis). Approximately 40% of children who present with allergic symptoms also have asthma, 50% have atopic dermatitis, and about 30% have allergic rhinitis. It is also important to obtain an environmental history of allergen exposure, including pets and tobacco smoke, as well as a family history of atopy.

The physical examination should be thorough. The skin should be inspected for atopic dermatitis and the lungs for evidence of asthma. The nasal mucosa should be examined with an otoscope. In the child with allergic rhinitis, the nasal mucosa is swollen, pale, and sometimes cyanotic with copious clear discharge. Nasal polyps, if present, should be noted. Although polyps are most often present on an allergic basis, they may occur with cystic fibrosis. A transverse crease across the nose (ie, allergic crease) can occur from repeatedly using the palm of the hand in an upward thrust on the nares to relieve itching and open the nasal airway (ie, allergic salute). Dark circles under the eyes (ie, allergic shiners) may be present from chronic periorbital edema and venous stasis. Morgan fold (ie, Dennie-Morgan fold), a wrinkle just beneath the lower eyelids, is present from early infancy and is associated with atopic dermatitis and allergic rhinitis. Adenoid facies (ie, allergic gape) is secondary to chronic mouth breathing during the first several years of age and results in a characteristic pattern of maldevelopment of facial bones, causing a high-arched palate, flat maxilla, and angulated mandible with a recessed chin and dental malocclusion (Figure 95.1). If affected, the conjunctivae are erythematous with a clear discharge and may have a follicular appearance. The mouth may reveal a high-arched palate from chronic mouth breathing, and hypertrophic lymphoid follicles in the oropharynx often are seen.

Classification of allergic rhinitis, although not as stringent as that of asthma, is important because it guides the choice of optimal therapy. According to the World Health Organization Allergic Rhinitis and its Impact on Asthma guidelines, allergic rhinitis is considered to be intermittent if symptoms occur fewer than 4 days a week or fewer than 4 weeks in duration, whereas persistent rhinitis is defined as symptoms occurring 4 or more days a week or 4 or more weeks

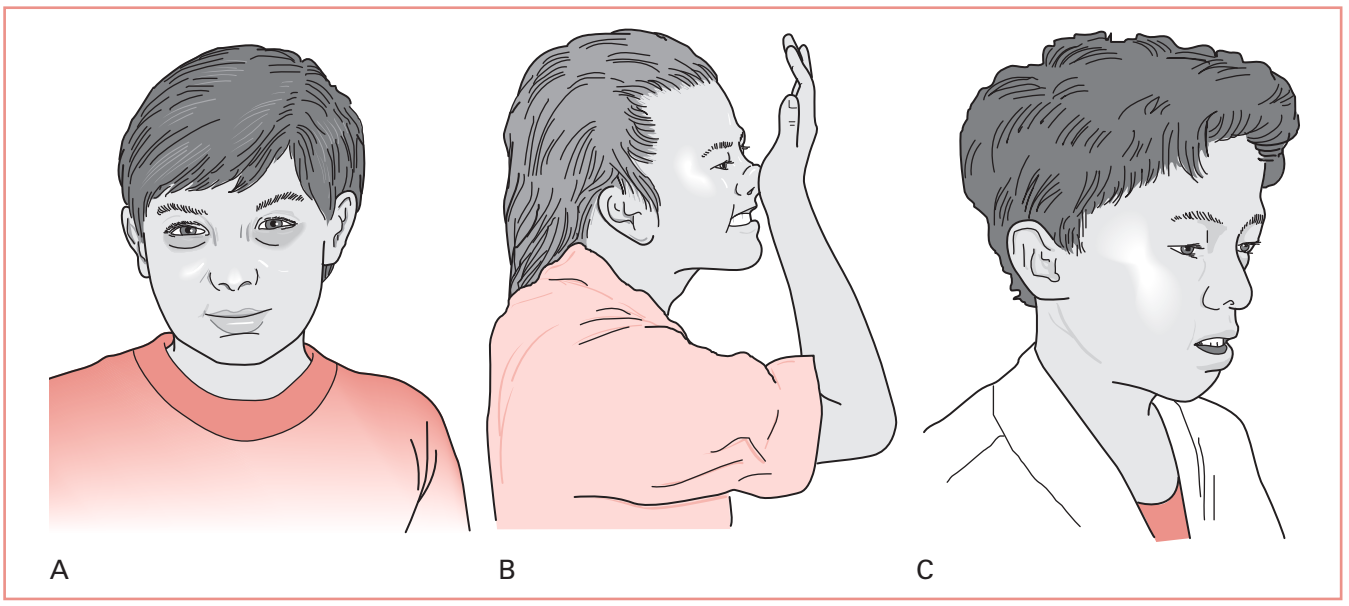

Figure 95.1. Characteristic facial features in children with allergic diseases. A, Allergic shiner. B, Allergic salute. C, Adenoid facies.

in duration. Further, mild allergic rhinitis is defined as having no sleep disturbances; normal activities, sports, and leisure; normal school or work; and no troublesome symptoms. One or more of these symptoms results in classification of moderate/severe persistent allergic rhinitis (Table 95.1). Thus, allergic rhinitis may be classified as mild intermittent, moderate/severe intermittent, mild persistent, and moderate/severe persistent.

Complications of chronic allergic rhinitis may be evident on physical examination, including chronic serous otitis, recurrent otitis media, hearing loss secondary to otitis, sinusitis, nasal polyps, sleep apnea, or dental malocclusion.

Urticaria and Angioedema

Because the most common causes of urticaria and angioedema in children are foods, medications, supplements, and viral infections, questions should focus on recent exposures to drugs, dietary changes, new soaps or detergents, environmental agents, and recent viral illnesses. Consideration should also be given to other serious conditions, such as collagen vascular disease and neoplasm. Laboratory tests usually are not required unless the history and physical examination are suggestive of a potential etiology; for example, a patient with urticaria, joint swelling, pallor, and fatigue requires testing for evidence of systemic lupus erythematosus and malignancy.

Anaphylaxis

In the patient with anaphylaxis, the history is focused on identifying an acute exposure to a foreign antigen (eg, medication, food, venom). Although most patients react within minutes to hours after exposure to the causative agent, anaphylactic reactions occurring many hours to days after exposure have been reported. Therefore, the history must be inclusive of this time frame.

Hemodynamically, patients have reduced peripheral resistance resulting from vasodilation and capillary leak. This results in warm skin and flushing. Compensatory increases in cardiac output result in tachycardia and bounding pulses. Patients often feel a sense of doom. Hypotension ensues if shock is untreated. Respiratory symptoms include airway edema with upper airway obstruction and stridor, and smooth muscle constriction results in wheezing and respiratory distress. Some patients have GI symptoms, including vomiting, abdominal discomfort or pain, and diarrhea. Most patients with anaphylaxis have skin manifestations (typically urticaria).

The most common cause of death from anaphylaxis is respiratory compromise followed by hemodynamic collapse.

Food Allergies

Diagnosing food allergy is not difficult if a reaction is clearly associated with ingestion of a specific food. Timing of the reaction is usually minutes to a few hours after ingestion. Diagnosis is less clear after a meal with multiple ingredients. Maintaining an accurate diet diary helps narrow the list of potential reactive foods. Negative food allergy test results via skin or in vitro serum IgE are reliable in ruling out a food; however, positive test results have limited predictive value unless values are high (Table 95.2). Therefore, a positive test result is suggestive of a food being responsible for a reaction, and confirmation should be pursued via an elimination period followed by food challenge. The double-blind, placebo-controlled food challenge is the diagnostic standard; however, it is impractical in most community clinical settings. National food allergy guidelines recommend using open food challenges to confirm a diagnosis. An absolute exception is in the patient with a serious systemic reaction (eg, anaphylaxis), in which case a strong history and a positive skin or serum test result is sufficient for diagnosis.

Table 95.1. Classification of Allergic Rhinitis

Frequency	Severity	
Not applicable	Mild: No sleep disturbances No impairment of activities, sports, leisure Normal school and work No troublesome symptoms	Moderate/severe (≥1 of the following): Sleep disturbance Impairment of activities, sports, leisure Abnormal school and work Troublesome symptoms
Intermittent (<4 days/week or <4 weeks' duration)	Mild intermittent: same symptoms as above	Moderate/severe intermittent: same symptoms as above
Persistent (≥4 days/week and ≥4 weeks' duration)	Mild persistent: same symptoms as above	Moderate/severe persistent: same symptoms as above

Derived from Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. *J Allergy Clin Immunol.* 2017;140(4):950–958 PMID: 28602936 https://doi.org/10.1016/j.jaci.2017.03.050.

Table 95.2. Specific Food Immunoglobulin E Levels and Likelihood of Clinical Reactivity

Food	IgE (kU/L)	PPV (%)	NPV (%)
Egg	7	98	36
Egg (<2 years of age)	2	95	—
Milk	15	95	53
Milk (<1 year of age)	5	95	—
Peanut	14	99	36
Soy	30	73	82
Fish	20	99	89
Wheat	26	74	87

Abbreviations: IgE, immunoglobulin E; NPV, negative predictive value; PPV, positive predictive value.

Adapted with permission from Adkinson NF Jr, Bochner BS, Burks AW, et al, eds. *Middleton's Allergy: Principles and Practice.* 8th ed. Philadelphia, PA: Elsevier Saunders; 2013.

Laboratory Tests

The diagnosis of an allergic disease can be made with a thorough history and physical examination when there is resolution of symptoms with empiric therapy. Additional tests are performed when the diagnosis is in question, to provide optimal avoidance strategies, and if allergen immunotherapy is needed. Testing may be necessary for the diagnosis of food allergy and further evaluation of urticaria and angioedema.

History of exposure followed by symptoms can be suggestive of causative agents; however, the combination of allergy testing with history improves the positive predictive value of a specific antigen causing the symptoms. For example, a patient with year-round indoor symptoms of rhinorrhea and nasal pruritus may be allergic to dust mites, cats, dogs, cockroaches, or mold. Subsequent allergen testing will elucidate which single allergen or combination of allergens is responsible for the symptoms. This results in a more focused and effective approach to environmental control. Allergen testing is also necessary if allergen immunotherapy is being considered.

Allergy testing may be achieved with in vivo skin-prick testing or in vitro specific IgE testing. Skin tests are sensitive and accurate. A positive test result indicates the presence of an antigen-specific IgE. Although skin testing may be less reliable in infants because their skin is less reactive than that of older individuals, these tests have been performed in infants as young as 4 months. Typically, fewer allergens are tested in children younger than 2 years compared with older individuals because those younger than 2 years of age have not been sensitized to a wide range of antigens. Currently, skin-prick testing is the recommended method for skin tests. Intradermal testing involving injection of allergen under the skin is used for testing of stinging insect allergy and various medication hypersensitivity and rarely is necessary for the diagnosis of inhalant or food allergen sensitization. When evaluating food allergy, intradermal testing should not be performed because of the risk of precipitating a systemic reaction.

In vitro allergen-specific IgE concentrations (ImmunoCAP, radioallergosorbent tests) in sera, which are also available for the laboratory assessment of allergies, provide a measure of the amount of IgE specific for individual allergens. Generally, in vitro tests have similar sensitivity and specificity as skin testing but are more expensive. In vitro tests have an advantage in that they can be performed on patients who are using medications that affect skin-testing reactivity, such as antihistamines and tricyclic antidepressants. Additionally, they are the preferred test in patients with poor skin reactivity, such as the very young and very old; those who do not have skin findings, such as atopic dermatitis and dermographism; and those who may have anaphylaxis to the allergens being tested.

For inhalant allergens, in vivo and in vitro tests have good negative and positive predictive values. Both tests have good negative predictive value for food allergy but positive predictive value of approximately 50%. For certain foods, very high levels of specific IgE have good positive predictive values (Table 95.2).

Other screening tests may include a nasal smear for eosinophil counts. More than 10% eosinophils is consistent with allergic rhinitis. Although serum IgE levels are elevated in 60% of patients with allergic rhinitis and asthma, they are not sensitive or specific and have limited value. Rhinoscopy in adults and older children provides a painless method to detect pathology not visible by anterior inspection via the nares. Such pathology includes identification of nasal polyps, deviated nasal septum, adenoidal hypertrophy extending into the nares, sinusitis, vocal cord edema, and polyps and potential masses. Computed tomography is clinically quite useful because it reveals structural abnormalities and mucosal disease, including findings within sinus cavities. The need for such information must be weighed against the high doses of radiation associated with computed tomography. Plain radiography of the sinuses is rarely indicated because of the limited ability to detail nasal anatomy and the high rates of false-negative results for sinusitis along with exposure to radiation.

Management

General Principles

Avoidance of allergen triggers is a natural means of controlling allergy symptoms without medication and should be encouraged in all patients with allergic disease. Currently, avoidance of allergen triggers is the only option available to patients with food allergy and anaphylaxis.

For patients with allergic rhinitis, conjunctivitis, and asthma, allergic triggers consist of perennial and seasonal allergens. Perennial allergens usually include house dust mites, warm-blooded animals with fur (eg, cats, dogs, rodents), cockroaches, and indoor pollens (usually molds). Seasonal allergens include outdoor molds as well as pollen from trees, grasses, and weeds. Effective environmental controls for these are outlined in Box 95.3. In addition to allergic triggers, nonallergic irritant triggers, such as tobacco smoke, automobile exhaust, smog, and perfumes, should be avoided.

Although environmental controls are safe and effective, they may be labor intensive, expensive, and, in rare cases, psychologically detrimental. For instance, removal of carpeting is difficult and expensive, especially in rented housing. Dust mite-proof coverings are expensive and cumbersome to wash in hot water weekly. Removal of family pets may result in psychological issues if children have become attached. Patients are more likely to institute environmental controls if evidence exists of allergic sensitization via skin-prick or blood tests.

Currently, no therapy is available to treat patients with food allergies except avoidance of the triggering food. Food avoidance should be undertaken only after a careful history, allergy testing, and a trial of food elimination and challenge to correctly identify the trigger. A poor history and false-positive testing can result in the implication of many foods, a draconian elimination diet, and undernutrition. The patient who is truly allergic to multiple foods will benefit from consultation with a registered nutritionist or dietitian. Additionally, such patients should be taught to read food labels to avoid offending foods.

Children generally lose sensitivity to milk, soy, egg, and wheat by school age. For instance, a large study noted that 85% of milk-allergic and 66% of egg-allergic children lost their sensitivity by 5 years of age. Only approximately 20% of patients with peanut allergy lose their sensitivity, and even fewer become tolerant of fish

Box 95.3. Environmental Control Strategies for Perennial and Seasonal Allergens

Dust Mites

- Cover mite reservoirs with mite-proof covers (eg, mattress, pillows, box springs, comforter).
- Wash linen in hot water once a week.
- Remove mite reservoirs, such as carpets, and if possible, stuffed toys.
- Use HEPA filter in conjunction with mite reduction strategies.
- Use vacuum cleaner that has HEPA filtration.

Pets (eg, dogs, cats)

- Do not get a warm-blooded furry pet (even if initially not allergic to cats or dogs), because children may sensitize to the pet later, at which time it will be difficult to remove the pet from the home.
- Bathing the pet once a week reduces the allergen load.
- Keep the child's room pet free or, if possible, have an outside cat or dog.
- Use of HEPA filter may help.
- Re-home the pet, if possible. (Note: Cat dander may linger for many months, and continuous house cleaning is required even after removal of the pet.)

Cockroaches/Rodents

- Use of boric acid for cockroach control is a pesticide-free strategy.
- Cockroaches and rodents often require professional extermination.

Mold

- Repair water damage.
- Reduce humidity.

Pollens

- Use HEPA filter.
- Close windows at night (plants usually pollinate in early morning).

Abbreviation: HEPA, high-efficiency particulate air.

and shellfish. Understanding the natural history of food allergies allows the clinician to liberalize the diet if retesting shows negative or reduced reactivity and a supervised food challenge is negative. The decision to challenge depends on the nutritional and social importance of a particular food.

Many patients with FPIES, allergic proctocolitis, and Heiner syndrome also outgrow their food hypersensitivities. The natural history of eosinophilic esophagitis is less clear. Rechallenge to more severe diseases, such as FPIES, must be performed in a monitored setting with staff who are competent in resuscitation.

Anaphylaxis is a medical emergency. Rapid reversal of cardiovascular or respiratory compromise is essential. Epinephrine is the first agent given to increase systemic vascular resistance, reverse bronchospasm, and reduce airway edema. A 0.01 mL/kg per dose of 1:1,000 aqueous solution is given intramuscularly in the lateral thigh. This route achieves high serum concentrations in the shortest time compared with other routes. Subcutaneous injection is no longer recommended. If symptoms progress or do not improve, epinephrine may be repeated in 5 to 10 minutes. Refractory symptoms have been managed with intravenous (IV) epinephrine diluted to 1:10,000. Because of the significant cardiac effects of IV epinephrine, however, cardiac monitoring must be instituted. Because vasoactive mediators result in capillary leak of fluids into the peripheral tissue, rapid volume expansion with normal saline or similar colloids should be instituted early, especially if response to epinephrine is poor. Administration of epinephrine must not be delayed; most deaths from anaphylaxis have been associated with delayed epinephrine administration.

Oxygen therapy should be instituted and bronchodilator drugs (eg, albuterol) given for bronchospasm and wheezing. H_1 and H_2 receptor antagonists, such as diphenhydramine and ranitidine, respectively, usually are given as well as systemic corticosteroids, such as methylprednisolone. Intravenous administration of these drugs ensures systemic delivery, especially if the patient is vomiting. However, antihistamines and corticosteroids are rapidly absorbed orally, and absorption of diphenhydramine is also good intramuscularly. These routes should be considered if IV access cannot be established in a timely fashion.

Because of the risk of a late-phase reaction or a biphasic reaction, the patient with anaphylaxis must be observed for a period of time, usually 4 to 8 hours. Administration of systemic corticosteroids and antihistamines does not adequately reduce the risk of late-phase reactions. The patient must be discharged with an epinephrine auto-injector and taught how to use it (0.15 mg for patients weighing <29.9 kg [<66 lb]; 0.3 mg for patients weighing ≥29.9 kg [≥66 lb]). Inpatient observation is appropriate for patients experiencing severe reactions or who need prolonged resuscitation, when triggers are unclear, if it is difficult to obtain an epinephrine auto-injector, and if the parents are not capable of recognizing anaphylactic symptoms or administering treatment. Medical alert bracelets should be issued if the offending agent is known.

Management of urticaria and angioedema should begin with the identification and elimination of the causal agent. Offending foods or medications should be avoided, underlying infections should be managed, and more serious etiologies, such as collagen vascular disease and malignancy, should be worked up and managed. Medications are required to manage bothersome symptoms and include H_1 and H_2 receptor antagonists and, in severe or persistent cases, corticosteroids. Tricyclic antidepressants are also used in adults and older children because of the potent antihistamine effects of these agents.

Medications

Avoidance of allergens and other triggers is sufficient in mild disease, but often, addition of medications is necessary when symptoms persist or are more severe.

Antihistamines or H_1 receptor antagonists have been used extensively in the management of allergic diseases and are effective in reducing symptoms of pruritus, rhinorrhea, and sneezing. They are less effective in relieving nasal congestion, although many patients report that their nasal congestion improves with these agents. These agents are also effective in reducing hives, swelling, and pruritus in urticaria and angioedema. First-generation antihistamines include

diphenhydramine, chlorpheniramine, and brompheniramine; although these agents are effective, they have significant sedating side effects. Even when administered at bedtime, patients show diminished concentration and attention the next day; sedating antihistamines can impair learning in schoolchildren. Newer H_1 receptor antagonists, such as loratadine, cetirizine hydrochloride, and fexofenadine hydrochloride, are less sedating and should be used as first-line agents in children. Some patients report decreased efficacy of these less-sedating antihistamines compared with older ones. Newer intranasal antihistamines, such as desmethylazelastine, have a rapid onset of action, are effective, and are quite safe but also are sedating.

Anti-inflammatory agents include intranasal corticosteroids, intranasal cromolyn sodium, and systemic corticosteroids. Intranasal corticosteroids have become the mainstay in the management of allergic rhinitis because of their powerful, broad anti-inflammatory properties and excellent safety profile. They are effective in reducing pruritus, rhinorrhea, sneezing, and congestion when used on a chronic preventive basis. Topical intranasal therapy has minimal to no effects on the hypothalamic-pituitary-adrenal axis when newer corticosteroids, such as fluticasone propionate and mometasone furoate, are used. Older agents, such as beclomethasone dipropionate, have more bioavailability, and children may experience small but significant growth delays. Cromolyn sodium is a mast cell stabilizer and has almost no side effects. Clinical efficacy is poor, however, and it is now used infrequently. Although most patients with allergic rhinitis do not require systemic corticosteroids, some patients who are refractory to treatment may benefit from a short course of oral corticosteroids, such as prednisone. Systemic steroids are usually used to control urticaria and angioedema and are mandatory in the management of anaphylaxis.

Alpha-adrenergic agents are used systemically as well as topically in the management of rhinitis. Oral agents, such as pseudoephedrine and phenylephrine, are effective but cause α-adrenergic side effects, such as tachycardia and jitteriness. Topical agents, such as oxymetazoline hydrochloride, are potent vasoconstrictors and can dramatically improve nasal obstruction; however, routine use for more than 3 to 5 days results in rebound congestion with persistent and worse symptoms (ie, rhinitis medicamentosa).

Leukotrienes have biologic effects similar to those of histamine and also recruit inflammatory cells into tissue. Therefore, the leukotriene receptor antagonist montelukast sodium can be used as monotherapy for the management of allergic rhinitis. Intranasal corticosteroids have better efficacy than montelukast sodium, but the latter is an oral agent that promotes better compliance. Additionally, allergic rhinitis is often comorbid with asthma, and montelukast sodium has the advantage of treating both conditions.

Normal saline washes provide a medication-free adjunctive treatment for allergic rhinitis, and their use has increased in popularity among patients.

Immunotherapy is quite effective for the long-term management of allergic rhinitis, allergic conjunctivitis, and stinging insect venom hypersensitivity and is also recommended for allergic asthma and atopic dermatitis when symptoms are not controlled using avoidance strategies and medications. This treatment is effective for symptoms caused by dust mites, pollens, animal dander, molds, and insect venom. Immunotherapy involves a series of injections with extracts of allergens specific for individual patients, producing tolerance to particular antigens. The mechanism of action of immunotherapy is related to the development of allergen-specific blocking antibody (ie, IgG), increased allergen-specific T regulatory cells, decreased lymphocyte cytokine response to an allergen, and decreased basophil histamine release in response to an allergen. The results of skin testing dictate which allergens to use. Initially, injections are given weekly with increasing doses until maintenance concentrations are achieved, at which point the injections are given once every 4 weeks. Immunotherapy is given in a supervised setting with an observation period of approximately 20 minutes, because of the small possibility for anaphylaxis.

In Europe, immunotherapy using sublingual delivery of antigens has been used effectively for many years without the need for injections. In the United States food allergen-specific therapies currently under investigation include oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and subcutaneous immunotherapy (SCIT). Early clinical trials for SCIT have shown efficacy in inducing oral tolerance to peanut allergy; however, most therapies have not been studied in humans. Oral immunotherapy and SLIT have been shown to have lower rates of systemic reactions than SCIT. Moreover, although most studies have reported that OIT has a higher efficacy for desensitization than SLIT, OIT has been found to have a higher incidence of side effects.

Additionally, epicutaneous immunotherapy, which solubilizes the allergen and enters via the stratum corneum, has been shown to be effective for cow's milk protein and peanut allergy and is in preclinical studies for egg allergy. Studies suggest that the risk for systemic reactions may be lower with epicutaneous immunotherapy than with SCIT, OIT, or SLIT.

Caveats About Treatment

Because patients with allergic rhinitis are repeatedly exposed to allergens, they may require use of anti-inflammatory agents, such as intranasal corticosteroids, as first-line therapy. Current guidelines for the United States recommend anti-inflammatory agents as first-line therapy for moderate/severe persistent disease and can be considered for mild persistent and moderate/severe intermittent disease. A patient may require long-term use of anti-inflammatory agents in combination with antihistamines (Figure 95.2).

Allergic conjunctivitis often coexists with allergic rhinitis. Control of nasal symptoms may result in improvement of eye symptoms, but ocular medications may also be required. Available medications include antihistamines, mast cell stabilizers, vasoconstrictors, and combination agents. The sight-threatening allergic ocular conditions of vernal conjunctivitis and atopic keratoconjunctivitis (both of which may cause corneal ulcerations) require prompt referral to an ophthalmologist.

In mild and sporadic cases of urticaria and angioedema, use of antihistamines is sufficient. With frequent and persistent eruptions,

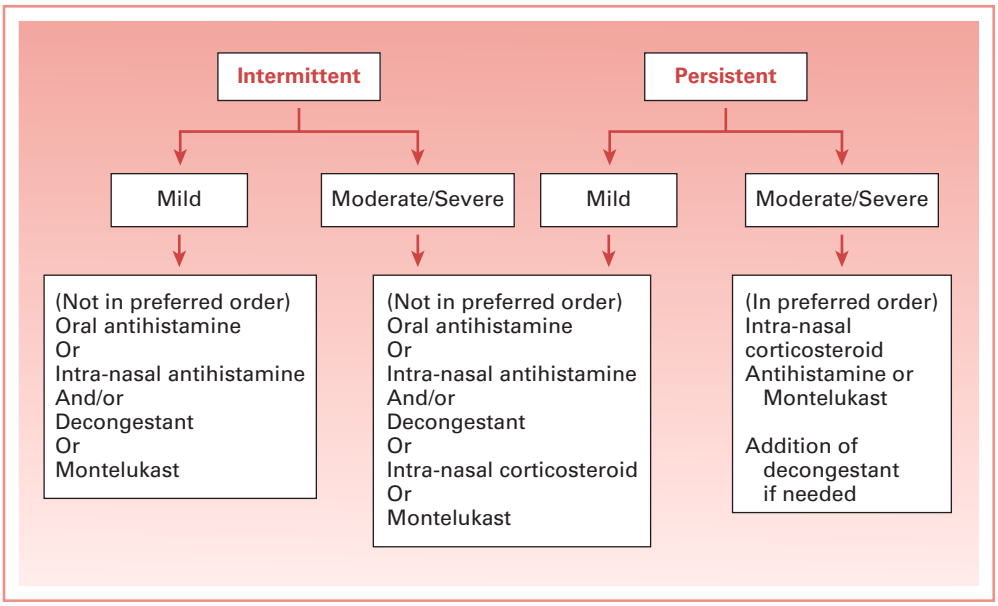

Figure 95.2. Allergic rhinitis treatment algorithm.
Adapted from Bousquet J, Schünemann HJ, Samolinski B, et al; World Health Organization Collaborating Center for Asthma and Rhinitis. Allergic Rhinitis and its Impact on Asthma [ARIA]: achievements in 10 years and future needs. *J Allergy Clin Immunol.* 2012;130[5]: 1049–1062, with permission.

however, the routine use of H_1 blockers with the addition of H_2 blockers may be required. In more severe and refractory cases, older first-generation antihistamines are necessary, with maximal dosages. In adults and older children, tricyclic antidepressants, such as doxepin hydrochloride, can be added when high doses of H_1 and H_2 receptor antagonists do not provide relief. Systemic steroids are effective in controlling symptoms of urticaria and angioedema; symptoms may recur after stopping, however, and patients may become dependent on them for relief.

Chronic urticaria and angioedema may last months to years, some in waxing and waning fashion. The patient with chronic idiopathic urticaria and angioedema must be counseled that the disease is not caused by an external agent. The aforementioned medications must be used long term to allow these patients to lead symptom-free lives until the pathology self-extinguishes.

Prevention

The cost of medical care, lost school days and workdays, disability from complications, and lives lost from allergic disease take a great toll on the population. Prevention significantly reduces the health burden.

Currently, evidence suggests that sensitization to foods can occur in the first 6 to 12 months after birth and even in utero. Strategies to avoid allergic foods during the third trimester and first year after birth have not diminished the prevalence of food allergies. Although breastfeeding is still recommended as the optimal form of nutrition for infants in the first 6 months after birth and studies have suggested mother's milk to have positive immune effects, data are insufficient to support strong associations between exclusive feeding of mother's milk and decreased development of specific allergic diseases (eg, eczema, allergic rhinitis).

In 2000, the American Academy of Pediatrics recommended delaying the introduction of certain highly allergenic foods in high-risk children based on early studies suggesting that delay may help prevent certain allergic diseases, specifically atopic dermatitis. Recent studies have suggested, however, that delayed introduction of solid foods may not only increase the risk of allergy, but that early introduction of certain foods (eg, egg, peanut) between 4 and 6 months of age may decrease the risk of allergy to that food. An interim guideline on the early introduction of peanut for infants at various risk levels was published in 2017 based on the Learning Early About Peanut allergy (LEAP) trial and other studies (Table 95.3); formal guidelines have yet to be developed, however.

Strategies to prevent development of inhalant allergies have not been universally effective. For the patient at risk for the development of allergic rhinitis and asthma, early avoidance of allergens is reasonable; however, this may merely delay sensitization until the patient is older. Strategies include removal of dust mite reservoirs (eg, carpets), covering of mattresses and pillows with mite-proof covers, not having a warm-blooded furry pet, and repair of water damage to reduce mold growth. Prevention of tobacco smoke exposure is essential.

Recently, the hygiene hypothesis has received attention. In this paradigm, exposure to bacterial components, such as endotoxin, results in a natural shift of lymphocytes from IgE-facilitating T helper type 2 cells and T helper type 1 cells. Global shifts away from endotoxin-exposing agrarian societies to more sterile urban societies reduces this shift and may result in the increase in atopy worldwide. A common misconception is that the child exposed to a dirty environment with multiple pets, respiratory infections, and dirt will be protected against atopy. The endotoxin-facilitated shift of T helper type 2 cells and T helper type 1 cells is likely to occur

Table 95.3. Recommendations for the Introduction of Peanuts in Allergic and Non-Allergic Infants

Extent of allergic symptoms	*Recommendation*	*Earliest age of peanut introduction*
Severe eczema, egg allergy, or both	Strongly consider evaluation by serum (peanut-specific IgE) and/or skin prick test and if necessary an oral food challenge. Introduce peanut based on results.	4-6 months
Mild to moderate eczema	Introduce peanut-containing foods	Around 6 months
No eczema or no food allergy	Introduce peanut-containing foods	Age-appropriate and in accordance with family preferences and cultural practices

Derived from DuToit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372:803-813.

in a narrow window in utero and during the first year after birth, however. Thus, exposure of older children to a dirty environment is unlikely to protect against atopy, and exposure of children with allergic disease exacerbates symptoms.

The method for preventing progression of allergic disease, sometimes referred to as allergic march, is immunotherapy. Immunotherapy against inhalant allergens in the child with allergic rhinitis significantly decreases the risk of asthma. The need for weekly, then monthly injections reduces the acceptance of this method, but the approval of SLIT may improve patient compliance.

Prognosis

Prognosis for the child with allergic disease is good. Some patients lose their allergy naturally or following immunotherapy. For others, allergic rhinitis, urticaria, and anaphylactic reactions persist throughout life on exposure to antigens. With appropriate management, however, the child can thrive and live a normal life. Methods to prevent development of inhalant and food allergies are less well understood; however, current research is focusing on strategies to prevent the development of inhalant and food allergies.

CASE RESOLUTION

The symptoms of rash, swelling, and wheezing after exposure to an antigen are suggestive of an anaphylactic reaction. Treatment with epinephrine, antihistamines, and systemic corticosteroids is clearly indicated. The girl should be observed for the occurrence of late-onset reactions. The child and family should be counseled to avoid any foods that contain peanuts. The parents should read all food labels and carry an epinephrine auto-injector (eg, EpiPen) at all times for emergency use. A medical alert bracelet indicating peanut allergy should be ordered and the patient and parents advised that she should always wear it. The patient should be referred to her primary care physician, who should consider referral to an allergist for further evaluation.

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CHAPTER 96

Wheezing and Asthma

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CASE STUDY

A 7-year-old boy is referred to the office after being seen in the emergency department for wheezing. He has been treated in the emergency department for wheezing 4 times in the past month and was once hospitalized for 3 days. The boy's father and paternal grandmother both have asthma.

The child's physical examination is remarkable for end-expiratory wheezing on forced expiration.

Questions

1. What are the most common causes of wheezing in infants and children?
2. What are the causes of reversible bronchospasm?
3. What is the pathophysiology of reversible bronchospasm?
4. How should the child with asthma be treated?

Recurrent wheezing is a frequent symptom of obstructive airway disease in children that may be caused by intrinsic or extrinsic compression of the airway, bronchospasm, inflammation, or defective clearance of secretions. Ten percent to 15% of infants wheeze during the first year after birth, and as many as 25% of children younger than 5 years present to their physician with wheezing during a respiratory illness. Most infants and young children with recurrent wheezing have asthma; however, a wide variety of congenital and acquired conditions can cause narrowing of the extrathoracic or intrathoracic airways and may present with wheezing. Reactive airway disease is the most common cause of wheezing in childhood. Childhood asthma typically falls into 1 of 3 categories: transient wheezing, late transient wheezing, and atopic wheezing.

Transient wheezing occurs in infants who are born with smaller caliber airways and who wheeze with viral lower respiratory tract infections and bronchiolitis. These infants do not have atopy and usually have no more wheezing by 3 years of age. Most patients with no atopic predisposition who wheeze in the early years after birth fall into this category. Late transient wheezing occurs in children who usually have a history of serious lung insult, such as severe respiratory syncytial virus (RSV) infections, and persistent wheezing beyond 3 years of age. These children also have no atopy, and symptoms usually slowly resolve over time. Atopic wheezing occurs in children with a strong atopic predisposition. Such children are most likely to develop asthma that persists throughout the school-age years.

Wheezes can originate from airways of any size, from the large extrathoracic upper airway to the intrathoracic small airways. In addition to narrowing or compression of the airway, wheezing requires sufficient airflow to generate airway oscillation and produce sound. Thus, the absence of wheezing in a patient who presents with acute asthma may be an ominous finding suggestive of impending respiratory failure. The audible musical or squeaking sounds noted with obstruction are caused by turbulence of the air as it is forced through a narrowed airway. Infants and young children are more prone to wheezing when they have airway obstruction because air forced through smaller airways is more turbulent than air forced through the larger airways of older children and adults. Infection-induced wheezing in children younger than 2 years is associated with RSV, especially in infants with passive exposure to smoke, and with rhinovirus in children older than 2 years. The most common causes of wheezing in infants and children are asthma, bronchiolitis, and pneumonia. Less common causes include congenital structural anomalies, gastroesophageal reflux and aspiration, cardiac failure, cystic fibrosis, foreign bodies, and vocal cord dysfunction (Box 96.1).

The modified Asthma Predictive Index (mAPI) is a clinical instrument used to predict persistence of asthma. Predictive factors include wheezing before 3 years of age and the presence of either 1 major risk factor (ie, parental history of asthma, personal history of atopic dermatitis, or patient sensitized to aeroallergen) or 2 of 3 minor risk factors (ie, patient sensitized to food, wheezing apart from colds, or eosinophilia). The mAPI has a positive predictive value of 76% and a negative predictive value of 95%. More than 80% of infants with a history of wheezing in the first postnatal years do not wheeze after 3 years of age.

Asthma is a common chronic disorder of the airways characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperreactivity, and underlying inflammation. Bronchospasm is reversible spontaneously or with treatment. In some patients, permanent alterations in the airway structure, referred to as *airway remodeling*, occur and are not prevented by or fully responsive to currently available treatment. Clinically, asthma is characterized by recurrent episodes of cough, chest tightness, dyspnea, prolonged expiration, wheezing, hyperinflation of the chest (ie, air trappings), use of accessory chest muscles (ie, retractions), and, in severe cases, cyanosis.

Box 96.1. Causes of Wheezing

Infection
- Bronchiolitis
- Pneumonia
- Bronchitis
- Laryngotracheobronchitis
- Bacterial tracheitis
- Toxocariasis
- Ascariasis

Reactive Airway Disease
- Asthma
- Exercise-induced asthma
- Anaphylaxis
- Nighttime cough asthma
- Toxic exposure (eg, smoke, organophosphate poisoning)
- Allergic aspergillosis

Laryngeal Dysfunction
Congenital Structural Anomalies
- Vascular rings
- Bronchiectasis
- Lung cysts
- Laryngotracheoesophageal cleft
- Tracheobronchomalacia

Defective Secretion Clearance
- Cystic fibrosis
- Immotile cilia syndrome

Tumor (Mediastinal)
- Lymphoma
- Teratoma
- Neuroblastoma
- Thymoma

Chronic Aspiration
- Gastroesophageal reflux
- Bulbar palsy
- Tracheoesophageal fistula

Other Causes
- Bronchopulmonary dysplasia
- α_1-Antitrypsin deficiency
- Pulmonary hemosiderosis
- Sarcoidosis

Foreign Body
Cardiac Disease
Immunodeficiency

Epidemiology

Asthma is the most common chronic childhood illness. In 2017, the National Health Interview Survey noted that 9.5 million children had asthma. Asthma is the leading cause of emergency department (ED) visits, hospital admissions, and school absenteeism. Over the past several decades, the prevalence of asthma has increased worldwide, an increase that varies from 40% in some areas of the United Kingdom and Australia to 3% in Indonesia, China, and India. Asthma prevalence, mortality, and hospitalization rates are higher in blacks than in whites. One-third of patients initially experience symptoms in the first year after birth, and 80% are diagnosed by the time they reach school age. In the United States, asthma is a leading diagnosis for children admitted to children's hospitals. Hospitalization rates have remained relatively stable, with lower rates in some age groups but higher rates in children 0 to 4 years of age. Additionally, asthma is a major cause of school absence; 23% of school days missed can be attributed to asthma. The male-to-female ratio is 2:1 until age 10 years and is equal from ages 10 to 14 years; after puberty, asthma incidence is greater in girls and women.

In recent years, the incidence of more serious disease in younger children and adolescents has increased. Low socioeconomic status is associated with an increase in asthma prevalence, morbidity, and mortality. Inner-city blacks are most at risk, but studies suggest that socioeconomic class and health care disparities only partially account for these differences.

Clinical Presentation

The child with asthma may present with acute symptoms of cough, shortness of breath, prolonged expiration, use of accessory muscles of respiration, wheezing, reports of chest tightness or congestion, hyperinflation of the chest, cyanosis, exercise intolerance, tachycardia, and abdominal pain.

Wheezing may be audible and detected by the parent or guardian or may not be appreciated until the child is examined by a physician. The child with severe bronchoconstriction may have no wheezing because the flow of air is impeded; however, wheezing may occur after bronchodilator treatment resulting from partial opening of the airway.

Some children have cough, which may be nocturnal or recurrent as a predominant symptom. Some pediatric patients have symptoms, such as cough or wheezing, that are precipitated or exacerbated by exercise (Box 96.2).

Abdominal pain and vomiting also are common in younger children and may be followed by temporary relief of respiratory symptoms. During an acute asthma attack, a low-grade fever, profuse sweating, and fatigue from the hard work of breathing may be apparent.

Pathophysiology

Asthma is a chronic inflammatory disorder of the airways. The immunohistopathologic features of asthma include alteration and denudation of the airway epithelium, thickening of the basement membrane, fibrotic changes in the subbasement membrane, bronchial smooth muscle hypertrophy, edema and angiogenesis, mast cell activation, and inflammatory cell infiltration (ie, neutrophils, lymphocytes, eosinophils), which release mediators such as histamine, prostaglandin, leukotriene, and major basic proteins. These

Box 96.2. Diagnosis of Asthma in the Pediatric Patient

- Recurrent wheezing
- Shortness of breath
- Exercise intolerance
- History of allergies
- History of atopic dermatitis
- Nasal polyps
- History of nighttime cough

changes result in airway hyperreactivity, airflow limitation, respiratory symptoms, and disease chronicity. The limitation to the flow of air results from acute bronchoconstriction, airway edema, mucus plug formation, and airway wall remodeling. The unique anatomy and physiology of the lung in infants compared with adults predisposes infants to obstructive airway disease. These anatomic differences include reduced number and size of the alveolar pores and canals of Lambert, causing deficient collateral ventilation and a predisposition to atelectasis distal to the obstructed airway. Mucous gland hyperplasia favors increased intraluminal mucus production. Decreased smooth muscle in the peripheral airway results in less support and narrower airways. Decreased number of fatigue-resistant skeletal muscle fibers in the diaphragm, its horizontal insertion to the rib cage (versus oblique in adult), and a highly compliant rib cage increase the work of breathing in children. Decreased static elastic recoil predisposes to early airway closure during tidal breathing, resulting in ventilation-perfusion mismatch and hypoxemia.

Atopy, the genetic predisposition to the development of immunoglobulin (Ig) E–mediated response to common aeroallergens, is a predisposing factor for developing asthma. At least 50 genes influence susceptibility to asthma and its clinical expression. Sites located on chromosomes 6p, 12q, 5q, 11q, and 16p are known to be associated with allergic diseases and encoding for major histocompatibility complex, IgE, interferon, and cytokine.

Environmental changes, such as wind, temperature fluctuations, and increased exposure to allergens or air pollutants (eg, tobacco smoke, ozone, sulfur dioxide, nitrogen dioxide), and particulate matter (eg, diesel exhaust, biologic residues [eg, endotoxin]), may precipitate clinical attacks. Inhalant allergens, particularly indoors, play an important role. The most important allergens are house dust mite feces (Der p1 and Der p2), cat allergen (Fel d1), and cockroach saliva (Bla g2, Bla g4, and Bla g5). Other inhalant allergens, such as dog dander, outdoor fungus (ie, *Alternaria*), and some pollens, also play a role. Infections, particularly respiratory ones, are implicated, influencing not only the exacerbation of asthma but also its inception and persistence. Viral infections, such as RSV, parainfluenza, and rhinovirus, are the most frequent precipitants of asthma exacerbations in infancy. The frequency of lower tract respiratory infection during early childhood with these viruses is a strong independent factor in development of asthma. *Mycoplasma* and *Chlamydia* infections can cause wheezing and persistence of asthma. Emotional stress may also play a role in the exacerbation of asthma.

The physiological changes involved in asthma occur in 2 phases: early and late. An immediate response (early phase) to the offending agent causes edema and bronchial smooth muscle constriction that result in narrowing of the airway and plugging with secretions. Air is trapped behind the narrowed airways, resulting in altered gas exchange, increased respiratory rate, decreased tidal volume, and increased work of breathing. The late response, which occurs 4 to 12 hours after the initial symptoms, primarily involves infiltration of the airways with inflammatory cells. The end pathway in the disease process is obstruction to airflow. The pathophysiology of asthma is reviewed in Figure 96.1.

Differential Diagnosis

An extensive differential diagnosis of asthma is listed in Box 96.1. Most conditions are differentiated from asthma by the presence of associated symptoms or the child's response to bronchodilators.

Evaluation

History

A thorough history, including how the child and family are coping with the asthma, should be obtained (Box 96.3). If acute respiratory distress is present, an abbreviated history focusing on potential precipitating factors and medication use should be obtained first, saving the more detailed history for a later time.

Physical Examination

Vital signs, including pulse oximetry, should be obtained. Objective determination of pulmonary function involves measuring the peak expiratory effort. *Paradoxical pulse*, the difference between systolic arterial blood pressure during inspiration and expiration, is usually under 10 mm Hg. This difference may be increased during an acute asthma exacerbation, but the measurement is difficult in young children. Breath sounds, work of breathing, the inspiratory-expiratory ratio, use of accessory muscles, presence of retractions, quality of breath sounds (whether decreased), presence of prolonged expiration, and quality of wheezing should be carefully assessed (Table 96.1). *Polyphonic wheezing* (ie, many different pitches, starting and stopping at varying points in the respiratory cycle) and cough are strongly suggestive of asthma. *Monophonic wheezing* (ie, a single, distinct noise of 1 pitch and starting and stopping at 1 discrete time) and cough should always raise suspicion for large airway obstruction caused by foreign body aspiration, vascular ring, or tracheomalacia. The nose and associated nasal passages should be examined for secretions, edema, pallor, and polyps. The skin should be assessed for eczema and other rashes. The chest should be carefully checked for increased anteroposterior diameter of the chest wall, a sign of air trapping. Fingers should be examined for signs of digital clubbing, which is suggestive of a diagnosis other than asthma.

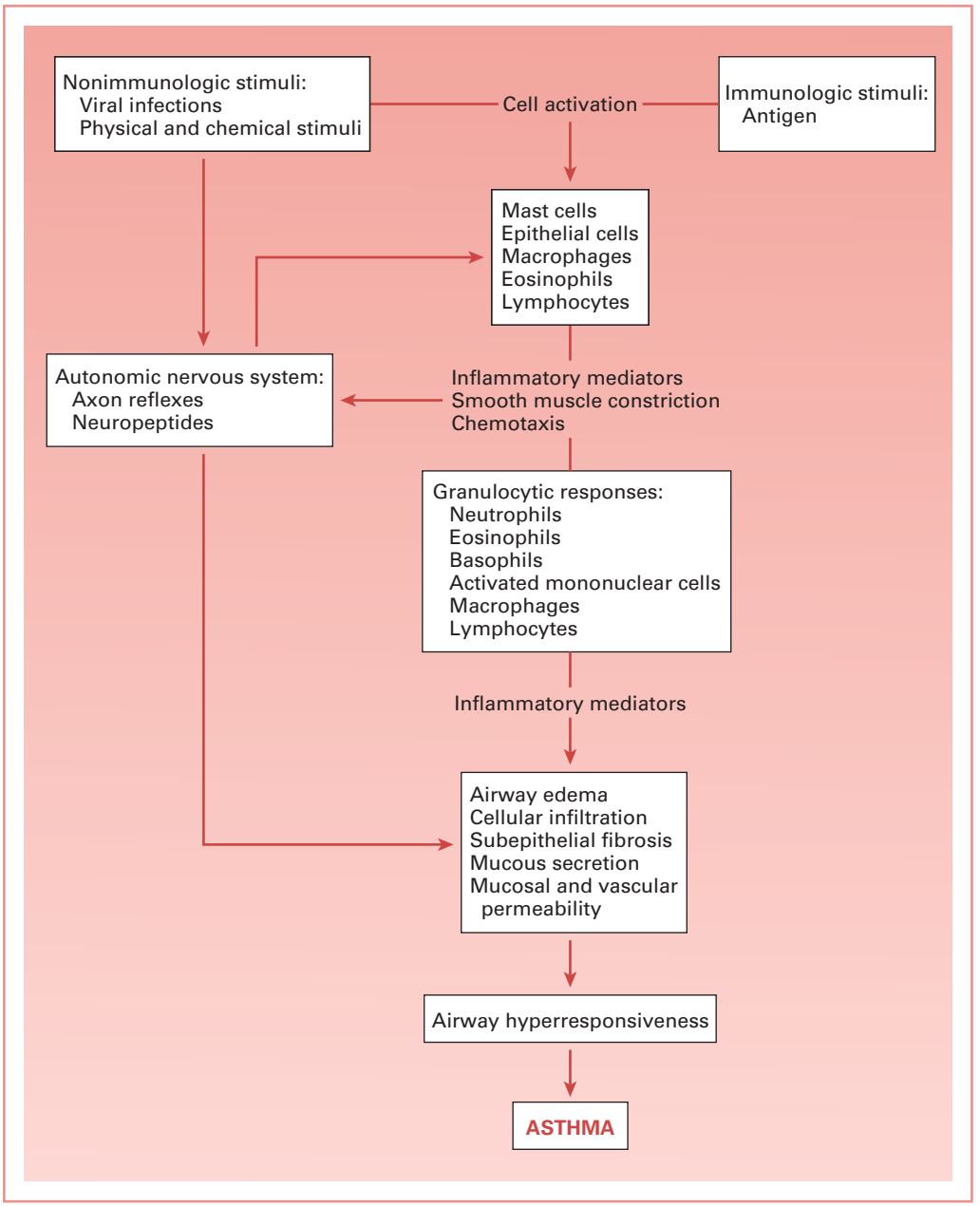

Figure 96.1. Proposed pathways in the pathogenesis of bronchial inflammation and airway hyperreactivity.
Reprinted from the National Asthma Education and Prevention Program. *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, MD: National Heart, Lung, and Blood Institute; 1991. NIH Publication No. 91-3042.

Laboratory Tests

Laboratory assessment of wheezing children is indicated if the diagnosis is unclear or to eliminate disorders that mimic asthma. Pulmonary function tests are noninvasive, objective, and cost-effective in the diagnosis and follow-up of patients with asthma. These tests can be performed in children older than 5 years with appropriate coaching. After the administration of an aerosolized bronchodilator, dynamic tests of airflow increase or return to normal. An improvement in forced expiratory volume in 1 second (FEV_1) greater than 12% is nearly diagnostic, but lack of improvement in FEV_1 does not preclude asthma. Exercise tolerance tests using a treadmill or free running followed by pulmonary function tests can be performed; a decrease greater than 12% in FEV_1 or 30% in forced expiratory flow is diagnostic for exercise-induced asthma. Peak flow meters, which measure forced peak expiratory flow, are useful in the office and at home to monitor expiratory flow rate. A decrease in peak expiratory flow may predict the onset of an exacerbation and suggests the need for early intervention, using additional drug therapy. A complete blood cell count with a differential count may be suggestive of infection or allergies. Peripheral eosinophil counts may be elevated in asthma. Pulse oximetry assesses the degree of oxygen saturation. Although not used as a parameter in North American asthma

Box 96.3. What to Ask

Asthma

- What symptoms (eg, wheezing, exercise intolerance) does the child experience?
- Does the child experience any nocturnal awaking or cough?
- What time of day and year do the symptoms occur?
- When did the symptoms begin? How old was the child?
- Are the symptoms associated with any particular activity? Does anything seem to trigger the symptoms?
- Are the child's activities limited in any way?
- How often do asthma attacks occur?
- What is the child's living situation? Are there pets in the home?
- Does anyone smoke in the home?
- Do asthma attacks cause the child to be absent from school?
- Does the child manage the condition at home with any particular treatments or medications?
- Has the child visited any urgent care facility or emergency department for treatment for asthma or related episodes in the past? Has the child had any hospitalizations?
- Does the child have a history of allergies?

guidelines for classification or assessment of asthma control, fractional exhaled nitric oxide (FeNO) has been shown to help differentiate diagnosis of asthma from other conditions that may mimic asthma, such as upper airway disease and reflux (ie, chronic cough). Additionally, some specialists use serial FeNO measurements to help wean patients off anti-inflammatory medications.

Sputum smear, stained with eosin-methylene blue agar, may show numerous eosinophils and granules from disrupted white blood cells, eosinophils, and epithelial cells. The presence of more than 5% to 10% eosinophils is suggestive of allergic inflammatory disease. Other findings in the sputum include Curschmann spirals, which are threads of glycoprotein; Creola bodies, which are clusters of epithelial cells; and Charcot-Leyden crystals, which are derived from eosinophils.

Total serum IgE is not as helpful as antigen-specific IgE in the diagnosis of asthma and is elevated in 80% of children with allergen-induced asthma. Allergy skin testing or serologic testing, such as radioallergosorbent testing, is indicated to identify potentially important environmental allergens. Allergens may play a significant role in asthma, and 85% of patients with asthma have a positive skin test reaction to common aeroallergens. Extensive laboratory testing should be reserved for the child with severe disease who may benefit from consultation with an allergy specialist.

Imaging Studies

The child with suspected asthma rarely requires chest radiography unless concern exists for other pathology. Radiographic findings may range from normal to hyperinflation, increased bronchial marking, and atelectasis, especially during acute exacerbation. Infiltration, pneumothorax, pneumomediastinum, and pneumonia are less common findings.

Management

The long-term goals of asthma therapy are listed in Box 96.4.

Assessment measures for asthma should include monitoring of the following: signs and symptoms, pulmonary function through peak flow or respirometry, quality of life or functional status, acute disease exacerbations, pharmacologic therapy, and satisfaction of the child and family with the asthma care.

Selecting the appropriate therapy for the patient with asthma depends on the age, disease severity (Table 96.2), and developmental level of the child; tolerance for a specific pharmacologic agent; and routes of administration. The pharmacologic treatment for symptom control and reduction of inflammation is predicated on the severity of the asthma, as categorized according to National Heart, Lung, and Blood Institute (NHLBI) guidelines. Box 96.5 contains an overview of these medications. Quick-relief

Table 96.1. Parameters Used to Estimate the Severity of Acute Asthma

Sign/Symptom	*Mild*	*Moderate*	*Severe*
Respiratory rate	Normal	Increased	Increased >2 standard deviations
Breath sounds	Normal (some end-expiratory wheezes)	Wheezing in inspiration and expiration	Decreased, with or without wheezing
Shortness of breath	None (can speak in sentences)	Can speak in phrases	Speaks only single words
Skin color	Normal	Pale	Pale to cyanotic
Work of breathing	Normal	Moderate retractions; some use of accessory muscles	Severe retractions, nasal flaring, use of accessory muscles
Pulse	Normal	Normal or increased	Increased
Level of consciousness	Normal	Normal	Diminished; may be lethargic or combative
Paradoxical pulse	<10 mm Hg	10–20 mm Hg	20–40 mm Hg
Oxygen saturation	>95%	90%–95%	<90%
Pulmonary function	80% of predicted	50%–70% of predicted	<50% of predicted

Box 96.4. Long-term Goals of Asthma Therapy

- Prevent chronic and disabling symptoms (eg, coughing, sleep disturbances, exercise intolerance, shortness of breath).
- Maintain normal or near-normal pulmonary function.
- Maintain normal activity levels.
- Prevent recurrent exacerbations and minimize the need for emergency department visits and admission to the hospital.
- Provide drug therapy that is effective with minimal side effects.
- Meet the expectations of the child and family for the care of asthma.
- Encourage self-management of asthma.

medications ("rescue meds") are used for acute exacerbations; the long-term control medications are used for chronic therapy. Nonpharmacologic measures are used in a preventive fashion and serve as an adjunct to drug therapy.

Short-term Management

Acute attacks can be managed in the office if the staff is prepared to manage a child in respiratory distress. Otherwise, the child can be referred to the ED. Equipment and supplies for resuscitation of infants and children must be available in offices in which care is provided for children with asthma.

The goal of therapy is to relieve airflow obstruction and prevent respiratory failure. All children with moderate or severe asthma should be placed in a position of comfort and given oxygen by nasal prongs or mask as tolerated. Assessment of work of breathing and the use of pulse oximetry help guide oxygen therapy. Nebulized β_2 agonists (eg, albuterol) are used until symptoms subside. The child may require drug therapy every 20 to 30 minutes. Not only are nebulized β_2-adrenergic agonists more effective than oral medications, they are associated with fewer side effects. Ipratropium bromide used in conjunction with a β agonist in the urgent care setting has been shown to reduce risk of hospitalization. Systemic corticosteroids, which help reduce the inflammation associated with clinical attacks, are indicated in most moderate and severe cases. Response to therapy is determined by clinical assessment of work of breathing, respiratory rate, objective changes in pulmonary function, and pulse oximetry. The child with incomplete response to initial therapy may require several hours of treatment or hospitalization.

Box 96.5. Pharmacologic Therapy: An Overview of Medications Used to Treat Asthma

Long-term Control Medications (Controller Class)

Corticosteroids

Most potent and effective anti-inflammatory medication currently available. Inhaled form is used in the long-term control of asthma. Systemic corticosteroids are often used to gain prompt control of the disease when initiating long-term therapy.

Cromolyn Sodium and Nedocromil

Mild anti-inflammatory medication. May be used as monotherapy in the setting of mild persistent asthma. Can also be used as preventive treatment before exercise or unavoidable exposure to known allergens.

Long-acting β_2 Agonists

Long-acting bronchodilator used concomitantly with anti-inflammatory medications for long-term control of symptoms, especially nocturnal symptoms. Includes salmeterol and formoterol.

Methylxanthines

Sustained-release theophylline is a mild-to-moderate bronchodilator used principally as an adjuvant to inhaled corticosteroids for prevention of nocturnal asthma symptoms. May have a mild anti-inflammatory effect.

Leukotriene Modifiers

Montelukast, a leukotriene receptor antagonist, or zileuton, a 5-lipoxygenase inhibitor, may be considered an alternative therapy to low doses of inhaled corticosteroids, or cromolyn or nedocromil, in the setting of mild persistent asthma.

Systemic Corticosteroids

- Used for moderate-to-severe exacerbations to speed recovery and prevent recurrence of exacerbations.
- Omalizumab (anti-immunoglobulin E), a recombinant DNA-derived humanized monoclonal antibody of the Fc portion of the immunoglobulin E antibody, binds to that portion, thereby preventing immunoglobulin E binding to its high-affinity receptor (FcεR1) on mast cells and basophils, resulting in a decrease in the release of mediators in response to allergen exposure.

Quick-Relief Medications (Reliever Class)

Short-acting β_2 Agonists

Albuterol and levalbuterol are therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchoconstriction.

Anticholinergic Agents

Ipratropium bromide provides additive benefit to inhaled β_2 agonists in acute exacerbations. May be an alternative bronchodilator for the patient who does not tolerate inhaled β_2 agonists.

Table 96.2. Classifying Asthma Severity

Components of Severity		*Intermittent*	*Persistent*		
			Mild	*Moderate*	*Severe*
Classifying Asthma Severity and Initiating Treatment (0–4 years of age)					
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting β_2 agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbation requiring oral systemic corticosteroids	0–1 per year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes per 12 months lasting >1 day AND risk factors for persistent asthma		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. Exacerbations of any severity may occur in a patient in any severity category.			
Recommended Step for Initiating Therapy (See Table 96.4 for treatment steps.)		Step 1: SABA PRN	Step 2: Low-dose ICS	Step 3: Medium-dose ICS and consider short course of OCS	
		In 2–6 weeks, depending on severity, evaluate level of asthma control achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			
Components of Severity		*Intermittent*	*Persistent*		
			Mild	*Moderate*	*Severe*
Classifying of Asthma Severity and Initiating Treatment (5–11 years of age)					
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting β_2 agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations FEV_1 >80% predicted FEV_1/FVC >85%	FEV_1 ≥80% predicted FEV_1/FVC >80%	FEV_1 = 60%–80% predicted FEV_1/FVC = 75%–80%	FEV_1 <60% predicted FEV_1/FVC <75%
Risk	Exacerbation requiring oral systemic corticosteroids	0–1 per year	≥2 per year		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy (See Table 96.4 for treatment steps.)		Step 1: SABA PRN	Step 2: Low-dose ICS	Step 3: Medium-dose ICS option	Step 3, Medium-dose ICS option or step 4
				Consider short course of OCS.	
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

(*continued*)

Table 96.2. Classifying Asthma Severity (*continued*)

Component of Severity		*Classifying of Asthma Severity and Initiating Treatment (≥12 years of age)*			
		Intermittent	*Persistent*		
			Mild	*Moderate*	*Severe*
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x week, but not nightly	Often 7x/week
	Short-acting β_2 agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily and more than once on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations FEV_1 >80% predicted FEV_1/FVC >85%	FEV_1 ≥80% predicted FEV_1/FVC normal	FEV_1 >60%, but <80% predicted FEV_1/FVC reduced 5%	FEV_1 <60% predicted FEV_1/FVC reduced <5%
Risk	Exacerbation requiring oral systemic corticosteroids	0–1 per year	≥2 per year		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. Exacerbations of any severity may occur in a patient in any severity category.			
Recommended Step for Initiating Therapy (See Table 96.4 for treatment steps.)		Step 1: SABA PRN	Step 2: Low-dose ICS	Step 3: Low-dose ICS + LABA	Step 4/5: Medium-/High-dose ICS + LABA
				Consider short course of OCS	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

Abbreviations: EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; OCS, oral corticosteroids; PRN, as needed; SABA, short-acting β_2 agonist.

Adapted from the National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH Publication No. 07-4051.

Long-term Management

The goals of long-term management are shown in Box 96.6.

Continuous and longitudinal primary care of children with asthma can profoundly affect the disease course. The primary care physician, child, and family must work together to achieve good control of symptoms. Prevention of exacerbations may be accomplished by removal of offending allergens. Minimization of exposure to known allergens and irritants has been shown to decrease symptoms and exacerbation. The most commonly implicated irritants are tobacco smoke; fumes from gas, oil, and kerosene stoves and wood-burning appliances; and sprays and strong odors. House dust mites are microscopic insects that feed on human scales, require humidity greater than 50%, and are found in stuffed furniture, carpets, and mattresses. House dust mite infestation can be reduced by encasing mattresses, blankets, and pillows in mite-proof covers; removing carpeting; and decreasing humidity to less than 50%.

Box 96.6. Therapeutic Goals for the Child With Chronic Asthma

- Maintain a normal, age-appropriate activity level
- Maintain near-normal pulmonary function
- Prevent symptoms such as exercise intolerance, chronic cough, and shortness of breath
- Prevent acute exacerbations of the disease that require acute therapy
- Minimize adverse effects of the drugs used to manage the disease
- Promote self-esteem and a sense of well-being

Allergen immunotherapy may be considered for the patient with asthma when evidence exists of a clear relationship between symptom and exposure to an allergen, and symptoms are poorly controlled with pharmacologic management (eg, medication ineffective, multiple medications are required, patient does not accept

or tolerate medication). Adherence to appropriate medications and in-home peak-flow measurement helps in prevention and control of asthma. Periodic assessment ensures appropriate therapy and compliance with treatment. The physician should make sure that the family can afford the necessary medications. During routine visits, home monitoring and therapy as well as any diaries and records should be reviewed, the child's and family's expectations about the course of the disease should be discussed, and all parties should be allowed to express their concerns about the development of a treatment plan. Other factors, such as rhinitis, sinusitis, and gastroesophageal reflux, which may influence the severity of asthma or the child's quality of life, should be assessed and treated appropriately.

Family members and the affected child should be given a written action plan based on the patient's personal best peak flow (Figure 96.2)

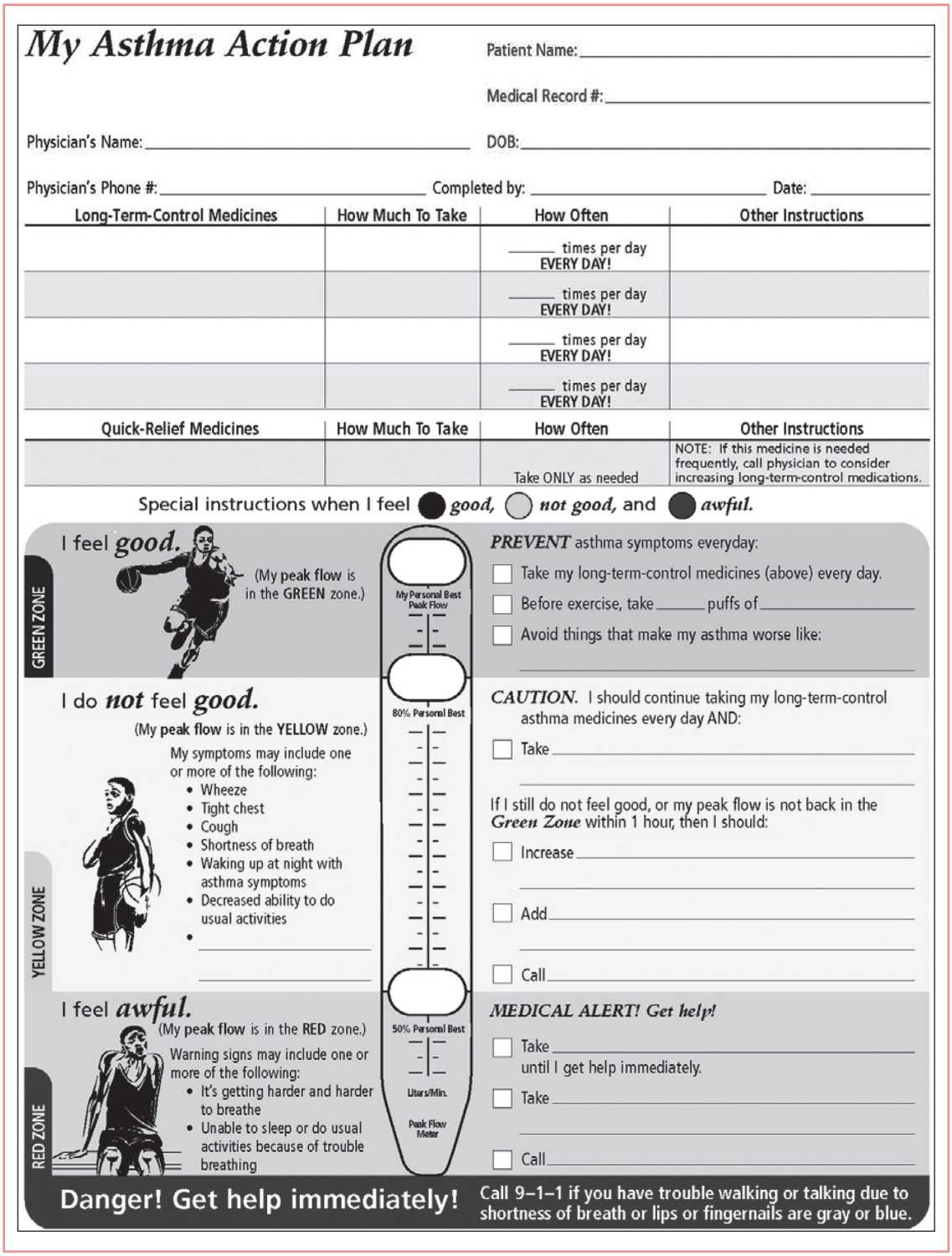

Figure 96.2. Asthma action/medicine plan.

Reprinted from National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program. Full Report 2007*. NIH Publication No 07-4051, Revised August 2007. https://www.nhlbi.nih.gov/sites/default/files/media/docs/asthgdln_1.pdf.

and instructed in the use of peak flow meters to indicate when medical treatment is necessary. Some meters have 3 color zones: a green zone, which indicates good airflow; a yellow zone, which signals the need for treatment; and a red zone, which suggests that a visit to the ED may be indicated.

Dynamic Monitoring and Treatment

Asthma rarely remains static over time. Symptoms wax and wane in severity and frequency depending on extrinsic and intrinsic signals (eg, viral infections), allergen exposure, and nonspecific triggers (eg, atmospheric conditions, cigarette smoke, air pollutants). Although assessment of underlying asthma severity is important and serves as a starting point in initiating therapy, assessment of asthma control is more important in dynamic treatment of the patient with asthma. The patient initially classified with intermittent asthma and only prescribed as needing bronchodilator rescue therapy may experience loss of asthma control for long periods of time. At a physician visit during this time, such a patient would be classified as having baseline/underlying intermittent asthma but currently very poorly controlled. Such a patient will require the addition of a long-term controller agent, such as inhaled corticosteroids (ICSs) (ie, step-up therapy). In juxtaposition, the patient with initially rated severe persistent asthma may experience long symptom-free periods (baseline/underlying severity: severe persistent, currently well controlled). In such a patient, therapy can be stepped down. Asthma control is rated similarly to severity (Table 96.3).

Pharmacologic Therapy

The 2007 NHLBI guidelines for asthma management are based on age group: children 0 to 4 years of age, children 5 to 11 years of age, and children 12 years and older (Table 96.4).

Asthma severity is categorized by impairment and risk. Impairment considers the frequency and severity of daytime and nighttime asthma symptoms, use of short-acting β_2 agonist for other than exercise-associated symptoms, effect on activities, and pulmonary function testing. Risk assesses the frequency of asthma exacerbations requiring the use of oral corticosteroids. The most severe level of symptoms, medication use, and other factors defines the level of severity, which determines the long-term approach to management. The patient with intermittent asthma may respond to short-acting bronchodilator as necessary, whereas the child with persistent asthma requires a controller medication (eg, ICS) to reduce inflammation.

Management of asthma is based on its severity and control. For intermittent asthma only, short-acting β_2 agonists are required on an as-needed basis to manage symptoms. Prophylactic use of β_2 agonists, cromolyn, or nedocromil may be administered for exercise-induced asthma before the onset of activity. For mild persistent asthma, daily anti-inflammatory medications (ie, controllers) are required with low-dose ICSs as recommended therapy or alternative monotherapy with cromolyn, nedocromil, or leukotriene modifier agents, such as montelukast. Short-acting β_2 agonists are used for acute exacerbations. For moderate persistent asthma, medium-dose ICSs or low-dose ICSs plus a second agent is recommended, depending on the age group. Second agents include long-acting β_2 agonists, leukotriene modifiers, and theophylline. For severe persistent asthma, usually high-dose ICS plus a second agent is required. Systemic corticosteroids may be required to gain asthma control in the patient with moderate to severe persistent asthma. In the patient with difficult-to-control asthma, especially one experiencing severe exacerbation despite optimal controller therapy, omalizumab has been shown to decrease risk of asthma attacks. Patients of all asthma severities require short-acting β_2 agonists for quick relief of symptoms and prevention of exercise-induced asthma.

Inhaled corticosteroids act topically on lung epithelium, inhibiting cell migration and activation and reducing airway hyperreactivity. They are the most effective anti-inflammatory medication for asthma. Inhaled corticosteroids reduce asthma symptoms, improve lung function, reduce acute exacerbations of asthma, and reduce the risk of death from asthma. Recent data show that ICSs are well-tolerated, safe medications at the recommended dosages.

Leukotriene modifiers interfere with the action of leukotrienes, inflammatory mediators released from mast cells, eosinophils, and basophils. Long-acting β_2 agonists provide at least 12 hours of bronchodilation by stimulating β_2 receptors in the airway, which increases the concentration of cyclic adenosine monophosphate, causing relaxation of airway smooth muscle. Long-acting β_2 agonists should never be used alone; instead, they should be used in conjunction with ICSs in the management of asthma.

A patient may be started at a higher level of medication at the onset to establish prompt control, after which step-down reduction should be implemented to reach the minimum medication necessary to maintain control (Table 96.3).

Biologics

Despite adherent use of ICSs, leukotriene receptor agonist, and long-acting β_2 agonist, a small but significant percentage of patients with asthma have poor asthma control and experience severe asthma exacerbations, such as asthma-related hospitalizations, ED visits, and oral corticosteroid rescue. Anti-IgE therapy (ie, omalizumab) has been used in adults with asthma for more than 20 years, and the 2007 NHLBI asthma guidelines recommend its use in patients age 12 years or older who require steps 5 or 6 of therapy (Table 96.4). Recently, anti-IgE therapy was approved by the US Food and Drug Administration for children as young as 6 years. Anti-interleukin-5 antibodies (ie, mepolizumab, benralizumab) have also been approved by the FDA for treatment of severe asthma and achieve similar results. Other monoclonal antibodies targeting cytokines in atopic asthma are projected to be approved, including anti-interleukin-13 and anti-thymic stromal lymphopoietin antibodies.

Table 96.3. Assessing Asthma Control

Components of Control		Assessing Asthma Control in Children (0–4 years of age) Classification of Asthma Control Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	>1x/month	>1x/week
	Short-acting β_2 agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Interference with normal activity	None	Some limitation	Extremely limited
Risk	Exacerbation requiring oral systemic corticosteroids	0–1 per year	2–3 per year	>3 per year
Components of Control		**Classification of Asthma Control (5–11 years of age)** **Well Controlled**	**Not Well Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Short-acting β_2 agonist use for symptom control (not prevention of EIB)	≥2 days/week	>2 days/week	Several times per day
	Interference with normal activity	None	Some limitation	Extremely limited
	Lung function	FEV_1 ≥80% predicted/personal best FEV_1/FVC >80%	FEV_1 = 60%–80% predicted/personal best FEV_1/FVC = 75%–80%	FEV_1 <60% predicted/personal best FEV_1/FVC <75%
Risk	Exacerbation requiring oral systemic corticosteroids	0–1 per year	≥2 per year	
Components of Control		**Classification of Asthma Control (≥12 years of age)** **Well Controlled**	**Not Well Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/month	≥4x/week
	Short-acting β_2 agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Interference with normal activity	None	Some limitation	Extremely limited
	Lung function	FEV_1 ≥80% predicted/personal best FEV_1/FVC >80%	FEV_1 = 60%–80% predicted/personal best FEV_1/FVC = 75%-80%	FEV_1 <60% predicted/personal best FEV_1/FVC <75%
	Validated questionnaires ATAQ ACQ ACT	 0 ≤0.75 ≥20	 1–2 ≥1.5 16–19	 3–4 N/A ≤15
Risk	Exacerbation requiring oral systemic corticosteroids	0–1 per year	≥2 per year	

Abbreviations: ACQ, Asthma Control Questionnaire©; ACT, Asthma Control Test©; ATAQ, Asthma Therapy Assessment Questionnaire™; EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; N/A, not applicable.

Adapted from the National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007.* Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH Publication No. 07-4051.

Table 96.4. Stepwise Approach for Managing Asthma by Age Group[a]

Age	*Step 1*	*Step 2[b]*	*Step 3[b]*	*Step 4[b]*	*Step 5*	*Step 6*
0–4 years	SABA PRN	Low-dose ICS Alternative: Cromolyn or montelukast	Medium-dose ICS	Medium-dose ICS + either LABA or montelukast	High-dose ICS + either LABA or montelukast	High-dose ICS + OCS + either LABA or montelukast
5–11 years	SABA PRN	Low-dose ICS Alternative: Cromolyn, LTRA, or theophylline	Low-dose ICS + either LABA, LTRA, or theophylline OR Medium-dose ICS	Medium-dose ICS + LABA Alternative: Medium-dose ICS + either LTRA OR theophylline	High-dose ICS + LABA Alternative: High-dose ICS + either LTRA OR theophylline	High-dose ICS + LABA + OCS Alternative: High-dose ICS + either LTRA or theophylline + OCS
12 years–adult	SABA PRN	Low-dose ICS Alternative: Cromolyn, LTRA, or theophylline	Low-dose ICS + LABA OR Medium-dose ICS Alternative: Low-dose ICS + either LTRA OR theophylline or zileuton	Medium-dose ICS + LABA Alternative: Medium-dose ICS + either LTRA OR theophylline or zileuton	High-dose ICS + LABA AND Consider omalizumab for the patient with allergies	High-dose ICS + LABA + OCS AND Consider omalizumab for the patient with allergies

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; PRN, as needed; SABA, short-acting β_2 agonist.

[a] At each step, in addition to medication, also address patient education, environmental control, and management of comorbidities.

[b] Steps 2-4 (5 years–adult): Consider subcutaneous allergen immunotherapy for the patient with persistent, allergic asthma.

Adapted from the National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH Publication No. 07-4051.

Prognosis

Asthma can result in significant morbidity and mortality if a child is not treated appropriately. The child without longitudinal primary care generally requires expensive therapy in EDs or inpatient settings. A significant number of individuals with asthma have fatal outcomes because of lack of timely and appropriate care. Nearly all these deaths are preventable.

CASE RESOLUTION

The boy requires not only medication but also education for himself and his family as well as longitudinal primary care. It is particularly important to assess possible environmental factors (eg, pets), exposure to smoke, and poor compliance with previous recommendations, all of which have contributed to his recurrent symptoms.

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CHAPTER 97

Cough

Nasser Redjal, MD, and Charles H. Song, MD

CASE STUDY

A 3-year-old boy presents with a cough of 4 weeks' duration. Previously, he has had cough with colds, but this cough is persistent and deeper in quality. The cough seemed to develop suddenly when he was playing at a friend's house. It occurs all day and disrupts his sleep at night. The boy has had no nasal congestion, fever, or sore throat. No one at home is coughing, and the boy has not traveled recently. Neither the boy nor his family has a history of allergies or asthma. Over-the-counter cough preparations have not helped relieve his symptoms. On physical examination, growth parameters are found to be normal. The child has a persistent cough with no respiratory distress. Chest examination reveals a normal respiratory rate, no retractions, and no use of accessory muscles, although diffuse expiratory wheezing is noted in the right lower lobe. The remainder of the examination is normal.

Questions

1. What are common parental concerns about cough?
2. What diagnoses should be considered in the child with persistent cough?
3. What findings from the history and physical examination are important in determining the etiology of cough?
4. What diagnostic workup is appropriate?
5. How should the child with cough be treated?

Cough is an essential protective reflex that allows for clearance of secretions and particulates from the airways. Its persistence can be distressing to the pediatric patient and often causes parental anxiety because of uncertainty of its etiology. Cough may be acute, subacute, or chronic. Acute cough lasts less than 2 weeks and often is associated with respiratory tract infections in children. Cough lasting 2 to 4 weeks is subacute, and cough lasting more than 4 weeks is persistent or chronic. In children 15 years and older as well as adults, *chronic cough* usually is defined as persistent cough lasting more than 8 weeks. Parental awareness as well as accessibility to medical care influences the timing of the initial visit to a physician or other health professional during the disease course. Cough may be classified as specific or nonspecific depending on whether an underlying etiology is found, and management of the disease is tailored accordingly.

Epidemiology

Cough is a common reason for pediatric office visits. In the National Ambulatory Medical Care Survey, 6.7% of pediatric office visits involved children who presented with cough. Typically, preschool age children have up to 8 upper respiratory infections with associated cough in a winter season. Persistent cough is also common, with some surveys demonstrating a prevalence of 5% to 10% in 6- to 12-year-old children, with higher rates in younger children. Cough is more common among boys than girls less than 11 years of age and may be less common in developing countries than affluent countries.

Clinical Presentation

Presentation varies considerably depending on the etiology of the cough. Most children have no evidence of respiratory compromise, but some present with respiratory distress. Depending on the underlying etiology, a child may manifest other symptoms of chronic lung disease, such as clubbing and failure to thrive, although most children are found to be in good health.

Pathophysiology

Coughing is a protective reflex that is automatically triggered by cough receptors found throughout the human airway, including the nose, paranasal sinuses, posterior pharynx, larynx, trachea, bronchi, and pleura. They are also found outside the respiratory tract in the ear canal, stomach, pericardium, and diaphragm (Figure 97.1).

Proximal airways (ie, larynx and trachea) are more sensitive to mechanical stimulation, and distal airways are more sensitive to chemical stimulation. Lung parenchymal (ie, bronchiolar and alveolar) tissue contains no cough receptors; thus, pneumonia may not produce a cough. Stimulation of any of these receptors by an irritant, whether mechanical, chemical, thermal, or inflammatory, can initiate the cough reflex. Impulses from stimulated cough receptors traverse afferent nerves (ie, vagus, glossopharyngeal, trigeminal, phrenic) to a "cough center" in the medulla, which itself is under some control by higher cortical centers. The cough center generates an efferent signal that travels down the vagus, phrenic, and spinal motor nerves to expiratory musculature, thereby producing

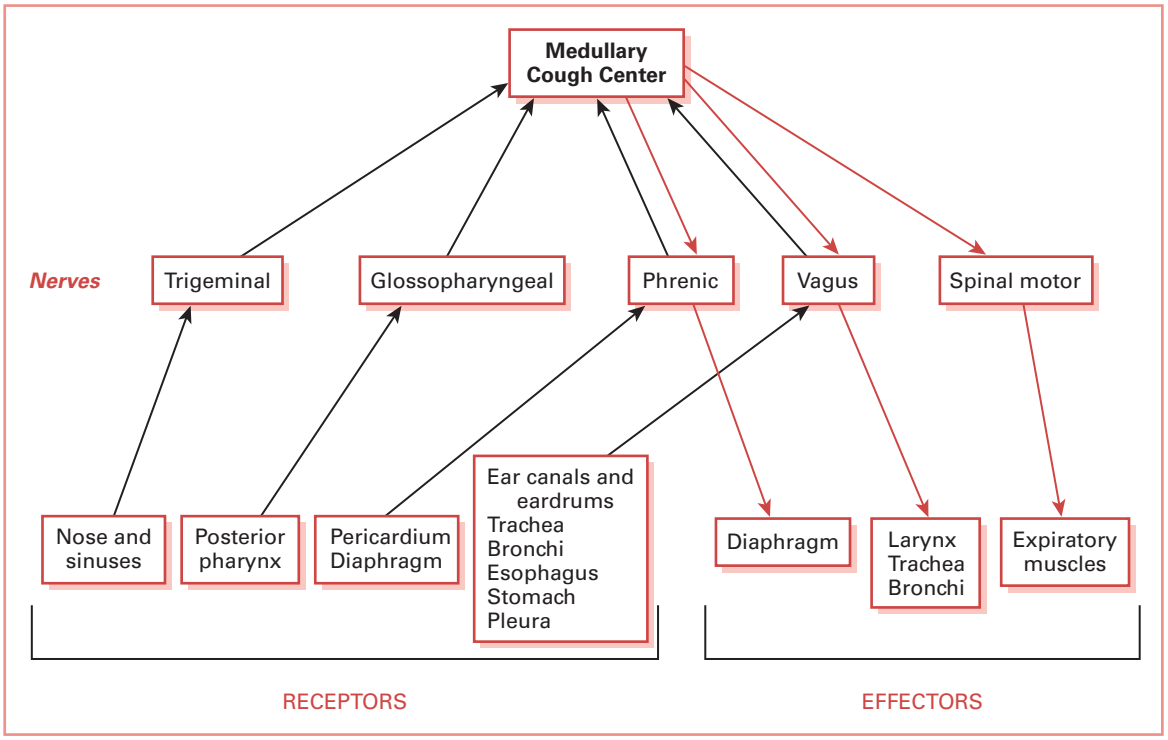

Figure 97.1. The cough reflex.

the cough. The cough center can be voluntarily stimulated or suppressed. Once initiated, the cough reflex propels excess mucus up the airways at the pressures of up to 300 mm Hg and at flows of up to 5 to 6 L/sec.

The cough experienced by patients may be broken down into 4 phases. First, the glottis opens with an inspiratory gasp. Second, the glottis closes with forceful contraction of the chest wall, diaphragm, and abdominal muscles. Third, the glottis again opens with release of airway pressure in an expiratory phase. Fourth, the chest wall and abdominal muscles relax. This process expels mucus or irritants from the airways, helping maintain lung health. The child who does not cough effectively may be at risk for atelectasis, recurrent pneumonia, and chronic airway disease from aspiration or retention of secretions.

Differential Diagnosis

Any pathology present along the airway from the nose to the alveoli can elicit a cough response; therefore, the list of differential diagnoses of cough is long (Box 97.1). Narrowing the list of causes can be accomplished by paying attention to several factors (Box 97.2). Typically, wet (ie, productive) cough tends to point to more specific diagnosis, whereas dry cough may be nonspecific.

The age of the child is an important determinant in the differential diagnosis. Cough presenting during infancy should prompt the physician to consider congenital chest anomalies, such as tracheoesophageal fistula, laryngeal cleft, vocal cord paralysis, and tracheobronchomalacia. Other congenital conditions include heart disease, which can produce a cough as the result of heart failure and pulmonary edema. Congenital mediastinal tumors induce cough if the tumor presses on the airway. Recurrent coughing or wheezing in infancy and early childhood associated with respiratory syncytial virus infection may be early signs of impending asthma in later childhood. Recurrent vomiting during infancy associated with chronic cough is suspicious for gastroesophageal reflux disease (GERD).

The duration of the cough is an important factor in determining the possible etiology. Most acute coughs are caused by a viral respiratory infection. The common viruses involved are rhinovirus, respiratory syncytial virus, human metapneumovirus, and adenovirus in infants and younger children; influenza and parainfluenza are common in children of all ages. All of these viruses affect the upper respiratory tract (common cold) more commonly, usually peaking on day 2 to 3 of illness and resolving in 2 weeks. Other causes of acute cough include asthma, bacterial upper respiratory infection (eg, pharyngitis, sinusitis), and pneumonia. The most commonly involved bacteria are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

In some children, especially those with underlying allergy or mild immune deficiency, cough may persist beyond 2 weeks after initial common cold symptoms appear. Virus may spread to the sinuses (ie, acute sinusitis) or to the lungs as pneumonia, bronchitis, or bronchiolitis. A secondary bacterial infection may also involve the sinuses and the lungs.

Cough lasting longer than 4 weeks is defined as chronic, and causes other than those associated with acute cough must be considered. In adolescents 15 years and older and adults, asthma, upper airway cough syndrome (eg, postnasal drip resulting from rhinitis or sinusitis), and GERD are the most common etiologies.

Box 97.1. Causes of Cough

Common

- Asthma
- Protracted bacterial bronchitis
- Upper airway cough syndrome
- Nonspecific cough

Less Common

Congenital Anomalies

- Tracheoesophageal fistula
- Laryngeal cleft
- Vocal cord paralysis
- Mediastinal masses
- Pulmonary malformations
- Tracheobronchomalacia
- Congenital heart disease

Infections (eg, Upper Respiratory, Sinusitis, Pneumonia)

- Viral
  - Adenovirus
  - Human metapneumovirus
  - Influenza
  - Parainfluenza
  - Respiratory syncytial virus
  - Rhinovirus
- Bacterial
  - *Chlamydophila pneumoniae*
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*
  - *Mycoplasma pneumoniae*
  - Pertussis
  - *Streptococcus pneumoniae*
  - Tuberculosis
- Fungal
  - Blastomycosis
  - Coccidioidomycosis
  - Histoplasmosis

Cardiac Disease

- Congestive heart failure
- Pulmonary hypertension

Chronic Disease

- Ciliary dyskinesia
- Cystic fibrosis
- Eosinophilic lung disease
- HIV infection
- Immunodeficiency syndrome

Allergic Conditions

- Allergic rhinitis
- Asthma
- Serous otitis media

Mediastinal Tumors
Foreign Body Aspiration
Gastroesophageal Reflux
Environmental Irritants
Psychogenic Cough
Drug-induced Conditions
Sarcoidosis
Tourette Syndrome (ie, Tics)

Box 97.2. Diagnosis of Cough in the Pediatric Patient

- Time of onset in infancy or early childhood: congenital lung and heart diseases, tumor, gastroesophageal reflux disease, protracted bacterial bronchitis
- Quality: dry, wet (ie, productive), brassy, honking
- Duration: acute, subacute, chronic, recurrent
- Timing: during the day, at night, on awaking, with exercise
- Fever or upper respiratory infection associated with infectious origin
- Symptoms of rhinorrhea, sneezing, wheezing, and eczema are suggestive of allergic asthma or rhinitis
- Failure to thrive (indicative of chronic disease)

In children younger than 15 years of age, the common causes of chronic cough differ and include asthma, protracted bacterial bronchitis (PBB), upper airway cough syndrome, and nonspecific cough. The diagnosis of cough-variant asthma can be made on the basis of spirometry (for older children), exhaled nitric acid (for older children), and positive bronchodilator response. Protracted bacterial bronchitis is now recognized as among the most common causes of chronic wet cough, especially in children younger than 5 years. The diagnosis is based on clinical criteria of chronic wet cough in the child without other respiratory causes and resolution of the symptom after a 2-week course of antibiotics. Pathogens identified on bronchoscopy, which generally is not necessary for diagnosis, coincide with the common bacteria for upper airway infection. The term "repeated PBB" is used in cases in which more than 3 episodes occur in a single year. Repeated PBB may result in bronchiectasis, and mild immunodeficiency (eg, specific antibody deficiency) should be ruled out.

Clinical findings not compatible with the aforementioned diagnoses warrant consideration of the many less common entities (Box 97.1). Certain infections are noteworthy. Pertussis in the infant and older child may present with cough for months without a classical whoop. Tuberculosis and fungal infections, such as coccidioidomycosis, should also be considered in endemic areas or high-risk populations.

An unexplained persistent cough, primarily in toddlers, may be the result of foreign body aspiration even if the initial aspiration was not observed. A history of choking episodes is absent in approximately 50% of patients, and the chest radiograph appears normal in approximately 20% to 40% of children in whom foreign bodies are noted on bronchoscopy. The foreign object acts as a chronic airway irritant that stimulates coughing, and it may be the cause of recurrent infections.

In older children and adults, drugs such as β-adrenergic receptor antagonists and angiotensin-converting enzyme inhibitors can also induce a chronic cough, likely by increasing the sensitivity of the cough reflex.

Patients previously treated with cytotoxic drugs or thoracic radiation are at risk of interstitial lung disease. Cough along with symptoms of pancreatic insufficiency, recurrent bacterial pneumonia, or failure to thrive are suspicious for cystic fibrosis.

Cough with a history of dyspnea or hemoptysis should prompt evaluation for organic lung disease. Hemoptysis also should raise concerns for an underlying condition, such as bronchiectasis,

cavitary lung disease (ie, tuberculosis, bacterial abscesses), congestive heart failure, hemosiderosis, neoplasm, foreign bodies, vascular lesions, endobronchial lesions, menstrual (ie, ectopic endometrial tissue) bleeding, and clotting disorders.

After all identifiable causes of cough have been ruled out, the diagnosis of nonspecific cough may remain. Unlike a wet cough associated with a specific diagnosis, a nonspecific cough tends to be dry and in most cases resolves gradually over many weeks. Although nonspecific cough is a diagnosis of exclusion, many patients have history of prior viral disease (ie, post-viral syndrome). These patients are best treated with observation and reassurance. Unresolving daytime cough in the otherwise healthy child, however, may be indicative of an underlying neuropsychogenic presentation (eg, tic, Tourette syndrome) and may necessitate referral to a pediatric behavior specialist.

Evaluation

History

A complete history should be obtained of the child who presents with cough (Box 97.3). All symptoms should be noted. Vomiting with cough can be indicative of phlegm production and accumulation of mucus in the stomach, with resultant delayed gastric emptying. In some children with a chief report of vomiting, the cough itself precipitates the vomiting. Posttussive vomiting is characteristic of, but not specific for, pertussis.

Box 97.3. What to Ask

Cough

- How old is the child?
- How long has the child had the cough?
- How frequently does the child cough?
- Does the cough occur at night?
- Does exercise make the cough worse?
- Do any factors, such as environmental irritants, seem to precipitate the cough?
- Does the child have any related infectious symptoms, including fever and nasal congestion?
- Does the child have any other symptoms?
- Has the child had any previous episodes of coughing or associated symptoms?
- Has the child lost weight recently?
- What is the child's birth history?
- Has the child had any pulmonary injuries?
- What is the child's immunization status?
- Does the child have a history of recent travel?
- Has a family member had similar symptoms?
- Does the family have a history of pulmonary disease or allergies?
- Has the child been treated with any medications for the cough? Have they helped?
- Is the child taking any other medications?

The presence of a nighttime cough can be important. Pathologic coughs, including those caused by sinusitis with postnasal drip, gastroesophageal reflux, and asthma, are more likely to occur at night than during daytime.

Physical Examination

A complete physical examination should be performed on all children who present with cough. Growth parameters and vital signs are assessed. Skin is examined for evidence of cyanosis or atopy. Facial petechiae or subconjunctival hemorrhage are indicative of particularly forceful coughing. Extremities are evaluated for fingernail clubbing, which is a sign of chronic pulmonary disease. The nose is assessed for evidence of congestion. Allergic disease produces pale, edematous mucosa, whereas infection results in a more inflamed mucosa. Tympanic membranes are examined and mobility is tested because otitis media can produce a chronic cough. A history of postnasal drip on the sinus area is suggestive of sinus disease. Tonsillar hypertrophy and pharyngeal cobblestone may be suggestive of an underlying allergic disorder as the basis of the cough.

The character of the cough is another important factor, because certain etiologies may be associated with a specific type of cough. A barking cough is consistent with laryngeal edema and croup. A cough with stridor may occur with proximal airway disease, such as laryngomalacia, tracheomalacia, or laryngotracheobronchitis, or in the presence of a foreign body. An inspiratory whoop is characteristic of pertussis or parapertussis. Staccato cough in an infant can be the result of infection with *Chlamydia trachomatis*. The psychogenic or habitual cough is a strange, honking sound, somewhat like that of a Canada goose, that is absent at night and typically is worst and most disruptive during school classes. Chronic paroxysmal cough triggered by exercise, cold air, sleep, or allergens is often seen in patients with asthma. In contrast, a chronic productive (ie, wet) cough is suggestive of a suppurative process and may require further investigation to exclude PBB, bronchiectasis, cystic fibrosis, active infection, immunodeficiency, or congenital malformation.

Respiratory effort, including the use of accessory muscles, is noted. Close attention is paid to breath sounds, taking care to determine whether abnormal sounds occur in the inspiratory or expiratory phase of respiration. Stridor is classically an inspiratory sound (see Chapter 71), whereas wheezing is usually an expiratory sound. Chronic cough and wheeze are often noted in combination. Even in the absence of a history of wheeze, it is important to listen carefully for this finding during the physical examination. Wheezing that is characterized by many different pitches and by starting and stopping at varied points in the respiratory cycle is termed *polyphonic* and in association with cough is strongly suggestive of asthma. Other causes of polyphonic wheezing include viral bronchiolitis, obliterative bronchiolitis, bronchiectasis, bronchopulmonary dysplasia, congestive heart failure, immunodeficiency, bronchomalacia, and aspiration syndromes.

Monophonic wheezing, that is, a single, distinct, 1-pitch wheeze that starts and stops at 1 discrete time, and cough are always suspicious for large airway obstruction caused by foreign body or by tracheomalacia. Extrinsic airway compression such as occurs with

vascular rings, lymphadenopathy, and mediastinal tumors is also associated with monophonic wheezing. Tuberculosis should be considered in the child with a monophonic wheeze, particularly in geographic areas in which the disease is prevalent.

Prolongation of the expiratory phase is associated with wheezing and also is indicative of airway obstruction. Abnormal breath sounds are localized, if possible. Because the character of the cough can establish the diagnosis, listening to the cough is likely the most important aspect of the physical examination. Description of the cough by a parent or guardian may be less diagnostic.

Laboratory Tests

Laboratory studies usually are not necessary in the management of cough. Studies should be ordered with the aim of proving or disproving the most likely diagnosis in a specific patient and should be guided by the history and physical examination.

If the history, physical examination, and chest radiography are suspicious for an infectious etiology, a complete blood cell count with differential and a purified protein derivative skin test or interferon-γ release assay for tuberculosis may be ordered. If possible, appropriate cultures or a rapid polymerase chain reaction-based DNA screening should be done. Most children swallow their phlegm, so sputum may be difficult to obtain. Gastric aspirates can sometimes yield a reasonable sputum specimen for culture; however, this is uncomfortable and is used only when absolutely necessary, such as in the management of tuberculosis. Nasopharyngeal cultures and rapid antigen detecting assays are useful if an infectious etiology is suspected, such as pertussis or various respiratory viruses. If a non-infectious diagnosis is suspected (eg, cystic fibrosis, immunodeficiency), other laboratory tests should be ordered as appropriate (Table 97.1). Allergy skin testing or allergen-specific immunoglobulin E serum testing may be indicated to exclude inhalant allergy.

Imaging Studies

Chest radiography consisting of anteroposterior and lateral views remains the mainstay of the diagnostic evaluation of cough and should be obtained when there are definitive signs on physical examination and chronic cough. A lateral decubitus view can provide additional information about pleural fluid or air trapping. Inspiratory and expiratory radiographs can be obtained if a foreign body is suspected. An area of inflation that does not deflate on exhalation or remains present in the decubitus position is suggestive of a foreign body. Congenital lobar emphysema and unilateral emphysema (Swyer-James syndrome) are rare causes of focal or unilateral hyperinflation. If a nodular pulmonary lesion is found on radiography, bronchoscopy may be the next step to further define the lesion. Bronchiectasis is a characteristic of cystic fibrosis, immunodeficiency, primary ciliary dyskinesia, chronic aspiration, and previous history of severe infection (most commonly adenovirus and pertussis). If sinusitis is suspected, computed tomography of the sinuses can be performed; however, it has poor specificity and carries increased radiation exposure. An upper gastrointestinal radiographic series or a pH probe study aids in defining gastroesophageal reflux if the cough is associated with meals or episodes of vomiting, or if the cough occurs at night.

Table 97.1. Tests to Consider for Evaluation of Chronic Cough

Etiology	*Recommended Tests*
Allergy	Allergy skin test or blood-specific immunoglobulin E test
Asthma	PFT, bronchial hyperreactivity test (eg, methacholine challenge test), exhaled nitric oxide, trial of asthma treatments
Ciliary dyskinesia	Ciliary function tests
Congenital anomalies	Bronchoscopy, chest radiography, CT/magnetic resonance imaging, angiography
Cystic fibrosis	Sweat chloride test, genetic test
Fungal infections	Coccidioidomycosis: antibody assay (precipitin, complement fixation) Histoplasmosis: antibody assay (complement fixation, immunoprecipitating) Serum and urine antigen detection
Foreign body	Chest radiography, bronchoscopy
Gastroesophageal reflux	Barium swallow, 24-hour pH recording, and BAL
Idiopathic pulmonary fibrosis, autoimmune disease	PFT and diffusion CT, autoantibodies
Immunodeficiency	Quantitative immunoglobulins
Pertussis, chlamydia, or other infectious etiologies	Cultures, serology, polymerase chain reaction testing
Purulent infection	Cultures (eg, sputum, BAL), chest radiography, CT, microbiology immunology, sweat test
Sinusitis	Imaging of sinuses on radiography or CT, nasal endoscopy
Tuberculosis	Mantoux test, interferon-γ release assay

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography; PFT, pulmonary function test.

In the child with asthma, the chest radiograph may be completely normal. In the cooperative child, further diagnostic testing with pulmonary function tests can be done to demonstrate airway restriction or obstruction. The most helpful test for the diagnosis of asthma may be the response to inhaled corticosteroids and bronchodilator.

Management

Therapy is focused on management of the suspected etiology. For cough-variant asthma without wheezing or respiratory distress, a trial of inhaled corticosteroids and bronchodilators is recommended for a period of a few weeks, after which response is assessed. Pretreatment and posttreatment spirometry, if available, provide additional evidence for a diagnosis of asthma. The young

child with wet cough with suspected PBB and bacterial sinusitis must be treated with appropriate antibiotics for at least 2 weeks. An immunodeficiency workup may be necessary for the child with recurrent history of PBB, sinusitis, and pneumonia. The child with cough that was preceded by choking should be evaluated for foreign body aspiration, whereas progressive cough with weight loss and fevers requires a workup for tuberculosis. Cough with seasonal sneezing and rhinorrhea may necessitate treatment for allergic rhinitis and postnasal drip. Symptoms may be the result of a combination of etiologies, and treatment of 1 pathology may result in only partial improvement; thus, management of the other causes is necessary for full resolution. For example, although therapy with intranasal steroid and antihistamines for 2 weeks results in partial resolution of cough, if GERD is also present the addition of a proton pump inhibitor may result in complete resolution of the symptom. The external ear is innervated by the vagus nerve, and removal of irritants from the external auditory canal may reduce the coughing. Medications that may provoke chronic cough, such as angiotensin-converting enzyme inhibitors, should be changed. For the irritant-induced cough, exposure to tobacco smoke and other irritants must be eliminated.

For many children, however, evidence of a specific disease may be lacking initially based on a detailed history, physical examination, imaging studies, and pulmonary function testing. Many physicians treating adult patients initiate empiric treatment for common etiologies based on American College of Chest Physicians 2006 guidelines: asthma, upper airway cough syndrome and GERD, even in the absence of findings. In children 15 years and older and adults with a normal history, physical examination, and chest radiography, it is reasonable to follow adult protocol. In younger children, the empirical approach also may be tried for the common entities for this age group: asthma, PBB, and upper airway cough syndrome.

When the cough is determined to be nonspecific based on ineffective empirical treatment and absence of other findings, it is necessary for the physician to maintain close communication with the patient and family to share the knowledge and reassure the parent(s) or guardian(s). Cough and cold preparations used to empirically manage allergic conditions in adults have been found to have unacceptable side effects in children. Expectorants and mucolytic agents in cough syrups have little effect on relieving cough. Most over-the-counter children's cough medications are marginally effective, provide no greater benefit than placebo, and may be associated with adverse or paradoxical reactions.

Chronic Cough

Viral infections are the predominant cause of acute cough in children, and reassurance may be the only treatment necessary until resolution of symptoms. Most children do not require treatment; benign agents, such as warm liquids with honey in children 1 year or older, often suffice.

Chronic cough often causes frustration and anxiety among patients and their parent(s)/guardian(s). The physician may be unable to provide a definitive etiology or timely relief of symptoms, resulting in patients seeking answers from multiple health professionals and trying many ineffective over-the-counter products. Key to effective management is developing a partnership with these patients and their families in seeking out the specific causes in a stepwise and thorough manner. It is important to inform patients and parents or guardians that irritation of the airways resulting in chronic cough often takes time to resolve even after the causes are properly managed and the improvement of cough symptoms should be measured in weeks rather than days.

Prognosis

With thoughtful evaluation, it is usually possible to identify the causes of acute and chronic cough. Most symptoms resolve with appropriate therapy. If the cough persists with treatment, alternate diagnoses should be considered.

CASE RESOLUTION

The child's cough began acutely and developed into a chronic cough. The boy has no history of allergies or symptoms consistent with an infectious process. Physical examination reveals localized wheezing. Chest radiography reveals hyperinflation of the right lung. The boy's symptoms and presentation are most consistent with foreign body aspiration, and he is admitted to the hospital for bronchoscopy.

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PART 7

Hematologic Disorders

CHAPTER 98

Anemia

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CASE STUDY

An 18-month-old girl is brought to the office with a 3-day history of cough, rhinorrhea, low-grade fever, mild scleral icterus, and pallor. During her first week after birth, she had hyperbilirubinemia of unknown etiology that required phototherapy. Her family history is significant for mild anemia in her father; the cause of his condition is unknown. A paternal aunt and grandfather had cholecystectomies while in their 30s.

On physical examination, the girl is tachycardic and tachypneic (no respiratory distress) with scleral icterus and pallor. Her spleen is palpable 3 cm below the mid-costal margin. The remainder of her examination is normal.

Questions

1. What hemoglobin and hematocrit values are associated with anemia?
2. What are the presenting signs and symptoms of children with anemia?
3. What is the appropriate initial evaluation of children with anemia?
4. What emergency situations in children who present with anemia should be recognized by the primary pediatrician?
5. When should a child with anemia be referred to a hematologist?
6. How is the family history relevant in the evaluation of anemia?

Anemia is caused by a reduction in hemoglobin concentration or red blood cell (RBC) count, with resulting decreased oxygen-carrying capacity of blood. Anemia is defined as a hemoglobin or hematocrit value that is less than 2 standard deviations below the mean for age and sex. With this statistical definition, 2.5% of the healthy population can be categorized as having anemia. These values vary throughout infancy and childhood as hematopoiesis evolves from fetal to adult type, and it is important to reference normal age- and sex-related values when interpreting a hemoglobin or hematocrit result (Table 98.1). Additionally, racial variation exists, with black children having lower average hemoglobin values than white children. Cardiopulmonary status should also be considered, because children with cyanotic heart disease or chronic respiratory insufficiency typically have hemoglobin values higher than the normal range and may be functionally anemic when the hemoglobin value falls, even if it is within the lower range of normal.

Epidemiology

Iron deficiency is the most common cause of anemia in childhood, occurring most frequently during late infancy through the first few years of age and again during adolescence. This prevalence pattern corresponds to periods of rapid growth and, when combined with poor dietary intake, can predispose to iron deficiency. Other contributing factors to iron deficiency include preterm birth, blood loss (most commonly menstrual or gastrointestinal [GI]), and GI conditions associated with decreased iron absorption.

Other epidemiologic factors that contribute to anemia are presented in Box 98.1. Anemias with a genetic etiology, including hemoglobinopathies (eg, sickle cell disease, thalassemias), RBC enzyme deficiencies (eg, glucose-6-phosphate dehydrogenase [G6PD], pyruvate kinase), and RBC membrane disorders (eg, hereditary spherocytosis), are commonly diagnosed in childhood. The highest incidence of sickle cell disease, thalassemia, and G6PD deficiency is in individuals of African, Mediterranean, and Southeast Asian descent within the "malaria belt" near the equator, likely reflecting an evolutionary advantage against malaria. Dietary factors can cause impaired hematopoiesis, as in iron, folate, or vitamin B_{12} deficiency. Ingestion of oxidants (eg, fava beans, medications) can trigger hemolysis in persons with G6PD deficiency. Ingestion of toxins, such as lead, can also result in impaired hematopoiesis. Lead poisoning occurs more commonly in children who live in cities and older housing. In an otherwise healthy child, viral infections can cause a pure red cell aplasia (eg, transient erythroblastopenia of childhood), an autoimmune hemolytic anemia, or an aplastic anemia. Children with congenital hemolytic anemias are at risk for hemolytic and aplastic crises associated with infectious illnesses.

Clinical Presentation

The clinical presentation of anemia depends on the age of the child, severity and cause of the anemia, and rapidity of onset (Box 98.2). Typically, anemia is detected on routine screening or as part of an evaluation for an acute illness in a child who is asymptomatic and has no significant physical findings. Children with gradual onset of anemia may be relatively asymptomatic, because time has allowed for compensatory mechanisms, such as plasma volume expansion and increased cardiac contractility, to take place. With severe

Table 98.1. Mean and Lower Limits of Normal for Hemoglobin, Hematocrit, and Mean Corpuscular Volume Determinations

	Hemoglobin (g/dL)		Hematocrit (%)		Mean Corpuscular Volume (fL)	
Age in Years	Mean	Lower Limit	Mean	Lower Limit	Mean	Lower Limit
0.5–1.9	12.5	11.0	37	33	77	70
2–4	12.5	11.0	38	34	79	73
5–7	13.0	11.5	39	35	81	75
8–11	13.5	12.0	40	36	83	76
12–14						
Female	13.5	12.0	41	36	85	78
Male	14.0	12.5	43	37	84	77
15–17						
Female	14.0	12.0	41	36	87	79
Male	15.0	13.0	46	38	86	78
18–49						
Female	14.0	12.0	42	37	90	80
Male	16.0	14.0	47	40	90	80

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Box 98.1. Epidemiologic Factors Related to Anemia

Genetic

- Autosomal-dominant: hereditary spherocytosis
- Autosomal-recessive: most Embden-Meyerhof pathway enzyme deficiencies (eg, pyruvate kinase deficiency), most hemoglobinopathies (eg, sickle cell disease, β-thalassemia)
- X-linked: G6PD deficiency

Ethnic

- Northern European: hereditary spherocytosis, pyruvate kinase deficiency
- Mediterranean (ie, Italian, Greek, North African): β-thalassemia, G6PD deficiency
- African: sickle cell disease, hemoglobin C, hemoglobin D, G6PD deficiency, α-thalassemia trait, hereditary elliptocytosis
- Southeast Asian: α-thalassemia, hemoglobin E, G6PD deficiency

Dietary

- Poor dietary intake (ie, iron, folate, or vitamin B_{12} deficiency)
  - — Iron (excessive cow's milk intake)
  - — Folate (excessive goat's milk intake)
  - — Vitamin B_{12} (vegan diet)
- Poor gastrointestinal absorption
  - — Iron, absorbed in duodenum (small bowel disease)
  - — Folate, absorbed in duodenum and jejunum (small bowel disease)
  - — Vitamin B_{12}, absorbed in terminal ileum (surgical resection, pernicious anemia, small bowel disease)
- Ingestion of oxidants (medications such as sulfa drugs, fava beans in G6PD deficiency)
- Toxins (lead)

Socioeconomic

- Living near highways: increased incidence of lead poisoning
- Poverty: associated with pica and lead poisoning

Infectious

- Malaria: heterozygous form of sickle cell disease, thalassemia, G6PD-deficiency confer protection
- Viral infections: transient erythroblastopenia of childhood, autoimmune hemolytic anemias, hemolytic crisis in patients with congenital hemolytic anemias
- Parvovirus: aplastic crisis in patients with hemolytic anemias
- Viral hepatitis: aplastic anemia

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

Box 98.2. Diagnosis of Anemia in Children

- Pallor, fatigue
- Scleral icterus
- Hepatosplenomegaly
- Lymphadenopathy
- Weight loss
- Congestive heart failure

anemia, easy fatigability and exercise intolerance can develop, and pallor, fatigue, headache, dizziness, and irritability may occur. Pallor, tachycardia, tachypnea, edema, and, in severe cases, outright congestive heart failure (CHF) may be noted on examination. Children with an abrupt drop in hemoglobin from blood loss or hemolysis present more acutely with signs of tachycardia, tachypnea, and possible hypotension and shock. If the anemia is caused by acute hemolysis, accompanying jaundice, icterus, and dark urine may be seen.

Pathophysiology

Erythrocytes develop from pluripotent stem cells within the bone marrow under the influence of various hematopoietic growth factors. Erythropoietin is the primary growth factor regulating RBC production and is produced primarily by renal interstitial peritubular cells. The primary function of the erythrocyte is the delivery of oxygen to tissues for aerobic metabolism, and hemoglobin is the main intracellular protein of the erythrocyte. Hemoglobin consists of 4 polypeptide subunits, each containing an active heme group that is capable of binding to an oxygen molecule. A normal erythrocyte has a life span of approximately 120 days and is subsequently removed from circulation as it passes through the reticuloendothelial system. Under steady state conditions, the daily 1% loss of aged erythrocytes is compensated by a normal active erythropoiesis. It is also important to note that red cell loss is greater (1.5%) and life span is shorter (90 days) during the late fetal and early neonatal period. Anemia occurs when an imbalance exists between erythrocyte production and destruction. It can arise from conditions resulting in decreased production, increased destruction (ie, hemolysis), or blood loss. Deficient production may be caused by nutrient deficiency (ie, iron, folate, vitamin B_{12}), bone marrow failure (acquired or inherited), or bone marrow infiltration (eg, malignancy). Increased destruction of erythrocytes can occur as a consequence of disorders intrinsic to the erythrocyte (eg, hemoglobinopathy, enzymopathy, membranopathy) or extrinsic factors (immune or nonimmune etiologies).

Differential Diagnosis

The differential diagnosis of anemia can be determined by considering the underlying mechanism of anemia, whether decreased production, increased destruction, or blood loss, and the size of the erythrocyte (ie, mean corpuscular volume [MCV]). The differential diagnosis of anemia based on pathophysiology and erythrocyte size can be found in Table 98.2 and Box 98.3. In determining the cause of

Table 98.2. Differential Diagnosis of Anemia Based on Pathophysiology

Pathophysiologic Mechanism	*General Diagnostic Features*	*Specific Diagnostic Features*
Decreased Production of RBCs	***Evidence of decreased production: ↓ reticulocytes***	
Marrow infiltration		Pancytopenia caused by bone marrow infiltration with leukemia, neuroblastoma, etc
Secondary to tumor infiltration		
Secondary to infiltration with nonmalignant cells		
Lipidoses		Lipid-filled macrophages
X-linked lymphoproliferative disorder		Hepatosplenomegaly
Osteopetrosis		Poor growth and bony encroachment on cranial nerve foramina
Decreased production of hematopoietic elements (bone marrow failure)		
Decreased RBC production only		
Constitutional: Congenital hypoplastic anemia		Multiple physical deformities
Acquired		
Acquired pure red cell aplasia		Associated with thymoma
Transient erythropenia of childhood		Associated with parvovirus infection
Decreased RBC and WBC production		
Constitutional		
Fanconi syndrome		Multiple physical deformities
Shwachman syndrome		Pancreatic insufficiency

(*Continued*)

Table 98.2. Differential Diagnosis of Anemia Based on Pathophysiology (*continued*)

Pathophysiologic Mechanism	*General Diagnostic Features*	*Specific Diagnostic Features*
Decreased production of RBCs, WBCs, and platelets (aplastic anemia)		
Constitutional		
Fanconi syndrome		Multiple physical deformities
Shwachman syndrome		Pancreatic insufficiency
Acquired: aplastic anemia		History of hepatitis B, toxin exposure, idiopathic
Dietary deficiency		
Iron deficiency		↓ MCV, ↓ MCH, ↑ RDW, ↓ serum iron, ↓ serum ferritin, excessive cow's milk intake
Folic acid deficiency		↑ MCV, ↑ RDW, megaloblastic marrow, low serum and RBC folate
Vitamin B_{12} deficiency		↑ MCV, ↑ RDW, megaloblastic marrow, low serum B_{12} levels, Schilling test
Vitamin C deficiency		Clinical scurvy
Protein deficiency		Kwashiorkor
Hypothyroidism		Low T4, elevated TSH
Increased Production (Hemolysis)	***Evidence of hemolysis: ↑ reticulocytes***	
Intrinsic RBC defects		
RBC membrane defects (spherocytosis, elliptocytosis)	Hyperbilirubinemia	+ Osmotic fragility, spectrin deficiency (hereditary spherocytosis)
RBC enzyme defects (G6PD deficiency, pyruvate kinase)	LDH (RBC)	+ Enzyme assays
Hemoglobin defects	MCV may be increased if reticulocytes high	
1. Qualitative defects (sickle cell anemia, HbC, HbE)		Hb electrophoresis
2. Quantitative defects (thalassemia)	MCV low with thalassemia	HbA_2 (β-thalassemia), targets cells
Extrinsic RBC disorders		
Immune		
Isoimmune hemolytic anemia (eg, ABO, Rh incompatibility)		+ Antiglobulin test
Autoimmune hemolytic anemia		
Idiopathic		+ Antiglobulin test
Secondary: postviral, autoimmune disorders, Evans syndrome		+ ANA Concomitant thrombocytopenia or neutropenia Concomitant renal disease (HUS)
Nonimmune (eg, DIC, HUS)		
Blood Loss	***Reticulocytes normal (acute loss), ↑↓ (chronic)***	
Overt (eg, splenic sequestration, gastrointestinal, nasal bleeding)	↑ Reticulocytes (chronic loss, not iron deficient)	Sickle cell anemia (splenic sequestration)
Occult (eg, bleeding Meckel diverticulum, pulmonary hemosiderosis)	↓ Reticulocytes (chronic loss, iron deficient); may have rapidly falling hematocrit	Pulmonary infiltrates iron deficiency (pulmonary hemosiderosis)

Abbreviations: ANA, antinuclear antibodies; DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red cell distribution width; TSH, thyroid-stimulating hormone; WBC, white blood cell.
Derived from Lanzkowsky P. *Manual of Pediatric Hematology-Oncology*. New York, NY: Churchill Livingstone; 1989:2–3.

Box 98.3. Differential Diagnosis of Childhood Anemias Based on Red Blood Cell Size

Hypochromic, Microcytic Anemia (Low MCV)

- Iron deficiency anemia
- Thalassemias
- Lead poisoning
- Anemia of inflammation or chronic disease

Normochromic, Normocytic Anemia (Normal MCV)

- High reticulocyte count
  - — Intrinsic red cell disorders
- Hemoglobinopathies (hemoglobin SS disease)
- Enzymopathies (G6PD, PK)
- Membranopathies (HS)
  - — Extrinsic red cell disorders
- Immune-mediated
- Nonimmune (thrombotic thrombocytopenic purpura [eg, hemolytic uremic syndrome])
- Low reticulocyte count
  - — Pure red cell aplasia (congenital hypoplastic anemia, TEC)
  - — Pancytopenia (marrow failure or infiltration)

Macrocytic Anemia (Increased MCV)

- Folate deficiency
- Vitamin B_{12} deficiency
- Congenital hypoplastic anemia
- Myelodysplastic syndromes
- Chemotherapy agents

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; HS, hereditary spherocytosis; MCV, mean corpuscular volume; PK, pyruvate kinase; SS, 2 sickle β-globin genes; TEC, transient erythroblastopenia of childhood.

anemia, the reticulocyte count is the most useful test in ascertaining whether the anemia is caused by decreased production or increased destruction. A reduced reticulocyte count indicates decreased marrow production, whereas an elevated reticulocyte count is strongly suggestive of hemolysis. Anemia based on erythrocyte size can be classified as microcytic (low MCV), normocytic (normal MCV), or macrocytic (high MCV). Microcytic anemias reflect a defect in hemoglobin synthesis and are most commonly the result of iron deficiency, thalassemia, lead poisoning, and chronic disease. Macrocytic anemias reflect a relative decrease in DNA synthesis during impaired erythropoiesis and are usually of nutritional origin (ie, vitamin B_{12} or folate deficiency). The many other causes of anemia commonly fall into the normocytic category and can be further divided based on the reticulocyte count. Etiology and erythrocyte size, the 2 systems for classification of anemia, are not mutually exclusive—simultaneous application of these systems enables the pediatrician to make a primary diagnosis of anemia and determine its probable causes.

Microcytic Anemias

Iron deficiency is the most frequent cause of microcytic anemia in childhood and occurs as a result of inadequate intake and increased requirements resulting from growth, blood loss, and malabsorption of iron. As iron deficiency evolves, depletion of iron stores occurs first, followed by iron-deficient erythropoiesis without anemia, finally resulting in iron deficiency anemia. The combination of rapid growth and inadequate iron intake is responsible for the common occurrence of iron deficiency anemia in toddlers and adolescents. Many young newborns and infants are spared because of adequate iron stores acquired in utero and the ingestion of iron-fortified formulas. Exclusively breastfed newborns and infants may require supplemental iron before 6 months of age and should be evaluated for anemia. Preterm newborns are the exception, because they have lower baseline iron stores. (Much of the iron stores are acquired by the fetus in the third trimester.) As iron stores become depleted during late infancy and cow's milk is introduced into the diet, the ever-growing older infant/toddler becomes at risk for iron deficiency. Excessive intake of cow's milk during the first few years after birth predisposes to iron deficiency because cow's milk has minimal bioavailable iron (<1 mg/L). Large intake of cow's milk results in early satiety and prevents adequate intake of other iron-containing foods. Iron deficiency is often further compounded by trace amounts of GI blood loss resulting from GI mucosal damage or cow's milk allergy enteropathy. Adolescents, particularly menstruating females, are also prone to iron deficiency because of the pubertal growth spurt and suboptimal dietary habits. In young infants and children older than 3 years, purely dietary iron deficiency is uncommon, and an evaluation for blood loss or malabsorption is warranted. Blood loss can occur as hematochezia or melena (eg, inflammatory bowel disease, diarrhea, Meckel diverticulum, polyp, ulcer), menorrhagia, epistaxis, hematuria, or rarely as pulmonary bleeding (eg, pulmonary hemosiderosis). Iron is absorbed primarily in the duodenum, and several dietary factors (eg, coffee, tea) as well as primary intestinal disorders can impair absorption (ie, celiac disease).

The *thalassemias* are a heterogeneous group of inherited anemias that are characterized by impaired or absent synthesis of the α or β chains that make up the normal adult hemoglobin tetramer. Beta-thalassemias are caused by a decrease in the production of β-globin chains. Anemia observed in the severe forms of β-thalassemia occurs as a result of ineffective erythropoiesis. This is because of the instability of excess α chains, which precipitate and cause oxidative damage to the cell membrane, resulting in premature destruction of the erythrocyte within the bone marrow. Erythrocytes that do survive in circulation have a shortened life span because of increased hemolysis. Severe forms (ie, compound heterozygous or homozygous state) are classified as β-thalassemia intermedia or β-thalassemia major depending on the clinical presentation and degree of anemia. Individuals with β-thalassemia major develop a severe anemia during the first year after birth because decreasing levels of fetal hemoglobin ($\alpha 2\gamma 2$) cannot be replaced by normal adult hemoglobin ($\alpha_2\beta_2$). Hemoglobin values fall to the range of 3 to 4 g/dL, and regular transfusions are required. Individuals with β-thalassemia intermedia usually present later in life and do not require early intervention with blood transfusions. In these patients, hemoglobin values are in the 7 to 8 g/dL range, and individuals may be intermittently transfusion dependent. Individuals with β-thalassemia

trait (ie, β-thalassemia minor), the heterozygous form, have a mild microcytic anemia with a hemoglobin that is approximately 2 g/dL below the normal mean for age. Clinically it is an asymptomatic anemia; however, it is of diagnostic relevance in that it must be distinguished from iron deficiency anemia, which may be a concomitant problem.

The α-thalassemias are caused by a decrease in the production of α chains and typically are milder than β-thalassemias. This is because the excess of β chains that occurs in α-thalassemia is more stable, resulting in less membrane damage and intramedullary erythrocyte destruction. Humans have 4 α-globin genes. Individuals with a deletion of 1 α-globin gene are silent carriers and are asymptomatic, with a normal hemoglobin value and MCV. Individuals with the 2-gene deletion have α-thalassemia trait and have a very mild microcytic anemia that is asymptomatic. Three-gene deletion causes hemoglobin H disease, a moderate chronic hemolytic anemia that may be intermittently transfusion-dependent. This occurs primarily in individuals of Southeast Asian descent. Four-gene deletion causes hydrops fetalis, an almost universally fatal condition that essentially results in fetal CHF and intrauterine demise.

Although lead inhibits heme synthesis and red cell function on many levels, microcytic anemia is a late finding of lead intoxication. Iron deficiency and lead poisoning often occur together, and the relationship between the two is complex. Pica is a risk factor for lead ingestion. In the presence of lead, iron uptake by the erythrocyte is diminished and iron deficiency increases lead retention and toxicity. Intestinal absorption and uptake of lead by red cells is decreased in the presence of iron. Additionally, iron deficiency and lead poisoning both tend to occur in individuals of lower socioeconomic status, and both are exacerbated by concomitant nutritional deficiencies.

Anemia of inflammation or chronic disease may occur in children with chronic infections, generalized inflammatory disorders (eg, rheumatoid arthritis), and some cancers. It is characterized by a decrease in serum iron and iron-binding capacity, an increase in ferritin, and the presence of iron in bone marrow macrophages indicating impaired iron mobilization from storage sites. Increased synthesis of hepcidin, an iron regulatory hormone, under the influence of inflammatory cytokines seems to be responsible for the hypoferremia observed in anemia of inflammation. Generally, anemia of inflammation is mild and may be microcytic or normocytic.

Macrocytic Anemias

Folate and vitamin B_{12} deficiency cause a macrocytic anemia as a result of defective erythroid precursor nuclear maturation and megaloblastic changes in the bone marrow. Folate is absorbed in the duodenum and jejunum and is widely available in meats, green leafy vegetables, and cereals. Because of the ubiquity of folate, dietary deficiency is uncommon; however, newborns and infants fed exclusively goat's milk are at risk because of the exceedingly low levels of folate in goat's milk. Individuals with chronic hemolytic anemias may also become folate-deficient because of high bone marrow activity and increased demand.

Vitamin B_{12} is available from animal sources and is actively absorbed in the terminal ileum in association with intrinsic factor. Vitamin B_{12} deficiency can occur in individuals with a strict vegan diet (or in exclusively breastfed newborns and infants of women following a strict vegan diet); however, it usually occurs as a result of malabsorption. Decreased absorption can occur in the setting of pernicious anemia secondary to decreased intrinsic factor, surgical resection (ie, following necrotizing enterocolitis), and GI disease.

Other causes of macrocytic anemias include congenital hypoplastic anemias, myelodysplastic syndromes, chemotherapeutic agents (eg, methotrexate), and hypothyroidism.

Normocytic Anemias

Normocytic anemias can be classified as hemolytic (ie, associated with a reticulocytosis) or hypoplastic (eg, reticulocytopenia). Hemolytic anemias can be further divided into disorders that are intrinsic or extrinsic to the RBC. Intrinsic RBC disorders include hemoglobinopathies, enzymopathies, and membranopathies.

Sickle cell disease is the most common hemoglobinopathy worldwide and is concentrated in individuals of African or mixed African descent. Inheritance of 2 sickle β-globin genes (ie, hemoglobin SS) is the most common form; however, other significant sickle syndromes include hemoglobin SC, $S\beta^+$ thalassemia, and $S\beta^0$ thalassemia. Hemolytic anemia and painful vasoocclusive episodes are the hallmarks of sickle cell disease. The anemia is generally well tolerated, with hemoglobin values ranging from 6.5 to 8.5 g/dL with an associated reticulocytosis (5%–15%). The 2 most common hematologic complications in sickle cell disease are aplastic crises and splenic sequestration, both of which can cause an acute drop in hemoglobin. Aplastic crises typically are the result of infection with parvovirus, which temporarily causes the complete cessation of red cell production. Splenic sequestration occurs most commonly in infants and young children with sickle cell disease, often in association with a viral illness. Large amounts of blood can be quickly trapped in the spleen, causing hypovolemia, shock, and massive splenomegaly. See Selected References for further information on and excellent reviews of this multisystem disorder.

Glucose-6-phosphate dehydrogenase deficiency, the most common RBC enzyme deficiency, is an X-linked recessive hereditary disease that renders the red cell susceptible to oxidant stress and hemolysis. Several variants have been defined; however, the most common variants are those associated with acute intermittent hemolytic anemias with exposure to oxidant stresses (eg, fava beans, medications). Variants associated with chronic hemolytic anemias are very rare.

Pyruvate kinase deficiency is the most common red cell enzyme defect and causes a chronic congenital hemolytic anemia. The degree of hemolysis is variable, ranging from a mild, fully compensated hemolytic process without anemia to a transfusion-dependent anemia. Individuals with severe hemolysis may be chronically jaundiced and may develop the clinical complications of chronic hemolytic states (eg, gallstones, transient aplastic crises in association with infections, folate deficiency, and infrequently, skin ulcers). *Hereditary spherocytosis* is the most common red cell membranopathy and is characterized by the presence of spherical-shaped erythrocytes on the peripheral blood smear. Increased membrane fragility caused by defects in proteins of the red cell membrane

(ie, spectrin, ankyrin, band 3, protein 4.2) results in membrane vesiculation and membrane loss and the assumption of a spheroidal shape. Hemolysis occurs when these spherocytes are then trapped within the spleen. Clinically, the degree of hemolysis varies from mild anemia to severe transfusion dependence. Complications of a chronic hemolytic state, such as gallstones, aplastic crises, and folate deficiency, also may be observed.

Hemolytic anemias that are caused by factors extrinsic to the red cell can be further classified as immune-mediated or nonimmune. Immune-mediated anemias may be the result of alloantibodies that occur in the setting of neonatal Rh or ABO incompatibility or transfusion reactions. Autoantibodies may occur in association with infection, autoimmune disorders, malignancy, or drugs. In children, autoantibodies (ie, warm immunoglobulin G, cold immunoglobulin M) are often seen in association with a viral illness or mycoplasma infection. Nonimmune hemolytic anemias include thrombotic thrombocytopenic purpura and macroangiopathy anemias caused by a myriad of etiologies, including infections, drugs, toxins, burns, and artificial heart valves.

Anemia resulting from reticulocytopenia can be congenital or acquired and can occur in isolation or in the setting of pancytopenia. *Congenital hypoplastic anemia* (ie, *Diamond-Blackfan anemia*) is a ribosomal disorder that causes a congenital pure red cell aplasia that presents early in infancy. The bone marrow typically shows red cell aplasia with a paucity of red cell precursors, and the red cells may be normocytic or macrocytic. Associated congenital anomalies, such as craniofacial anomalies, radial abnormalities, and renal and cardiac defects, occur in approximately 25% of affected individuals. Transient erythroblastopenia of childhood is an acquired anemia resulting from reticulocytopenia that typically occurs following a viral illness. Usual age of presentation is between 2 and 3 years in an otherwise healthy child, and complete recovery is the natural course. Aplastic processes, such as idiopathic aplastic anemia and hereditary Fanconi syndrome, usually present with neutropenia or thrombocytopenia in addition to anemia.

Evaluation

History

When evaluating an infant or child with anemia, the age, rapidity of symptom onset, MCV, and suspected underlying mechanism of anemia direct the history (Box 98.4). In most instances, it is important to inquire about dietary habits, with particular attention paid to the type and amount of milk ingested per day (number of bottles/ounces). Ingestion of more than 24 ounces of cow's milk per day should raise suspicion of iron deficiency anemia. Medication use, potential toxin ingestion (eg, lead), or a history of pica should be determined as well. Additionally, potential sources of blood loss (eg, hematochezia, melena, menorrhagia, hematuria, epistaxis, pulmonary) should be addressed. Acute onset of jaundice, icterus, or dark urine is suggestive of hemolysis and should elicit questions about possible triggers (eg, fava beans, medications, illnesses). A personal history of neonatal hyperbilirubinemia or a family history of anemia, gallstones, cholecystectomy, or splenectomy is suggestive of a congenital hemolytic anemia. Acute onset of hemolysis with a viral illness is consistent with an autoimmune hemolytic anemia. Individuals with a marrow failure syndrome often present with a prolonged history of increased fatigue and pallor, with occasional history of previous red cell transfusions prior to diagnosis. In acquired marrow failure states, such as aplastic anemia, the history is occasionally consistent with antecedent hepatitis, a viral syndrome, or, rarely, exposure to toxins (eg, benzene, toluene-containing compounds), or use of oral chloramphenicol, which is commonly available over the counter in Latin America.

Box 98.4. What to Ask

Anemia

- Does the child eat meat?
- Does the child drink too much milk (>24 oz/day)?
- Has the child had any bleeding recently?
- Has the child had a recent illness?
- Is the child taking any medications?
- Have the child's eyes appeared yellow?
- Does the child have a family history of anemia, jaundice, gallstones, or splenectomy?
- Did the child or siblings have jaundice at birth requiring phototherapy or exchange transfusion?
- Was the child born preterm, and if so, how early?

Physical Examination

Most children who present with anemia have a normal physical examination. Depending on the degree of anemia, pallor, tachycardia, or tachypnea may be present. In severe cases of anemia (ie, hemoglobin <3 g/dL) with chronic onset and in moderate anemia (ie, hemoglobin 3–7 g/dL) with acute onset from blood loss, CHF can occur. Other physical findings are unique to certain red cell disorders. Infants with sickle cell disease may present with dactylitis, a form of painful crisis that manifests as swelling of the digits associated with pain and sometimes fever. Splenomegaly can occur with sickle cell disease (in younger children, prior to autosplenectomy), β-thalassemia major and intermedia, and red cell membrane disorders, most commonly hereditary spherocytosis. In children with severe chronic hemolysis, regardless of etiology, classic facies (often called thalassemic facies) with frontal bossing and flattened nasal bridge can occur, caused by thinning of the facial bones from brisk intramedullary hematopoiesis. Children with congenital hypoplastic anemia or Fanconi syndrome may have physical anomalies, such as thumb or radial abnormalities, short stature, cardiac or renal anomalies, and developmental delay. Aplastic anemia or malignant infiltration of the bone marrow may present with concomitant neutropenia and thrombocytopenia. In the patient with neutropenia (ie, absolute neutrophil count <1,000/mL), signs of fever or infection may be present. If the patient is also thrombocytopenic, bruises, petechiae, and mucosal bleeding from the mouth, nose, and GI tract may also be present. With malignancy, such as leukemia, lymphadenopathy and hepatosplenomegaly may also be observed. Severe

Vitamin B_{12} deficiency can result in neurologic findings such as ataxia, impaired vibratory sensation, or even psychiatric symptoms.

Laboratory Tests

Complete blood cell count and peripheral blood smear provide a wealth of information and should be evaluated closely to narrow the differential diagnosis. The first step is to determine if the child is truly anemic by referencing the normal hemoglobin and hematocrit values for the child's age and sex. The second step is to evaluate the red cell indices. The MCV is a direct measure of red cell size and allows for classification of the anemia as microcytic, normocytic, or macrocytic (Figure 98.1). The mean corpuscular hemoglobin is a calculated value that typically parallels the MCV. The mean corpuscular hemoglobin concentration is a measure of the red cell hydration status and is useful when elevated, because an elevated level indicates the presence of spherocytes. The red cell volume distribution width reflects the variation in red cell size; typically, it is normal in patients with thalassemia trait and elevated in the setting of iron deficiency. The RBC count can be useful because it is typically elevated (>5 million/mL) in a child with thalassemia trait and decreased in iron deficiency anemia. Review of the white blood cell and platelet count provides information as to whether other cell lines are affected. The peripheral blood smear provides information on RBC morphology characteristic of different red cell disorders (eg, sickle cells, spherocytes, elliptocytes, schistocytes, bite cells). The presence of polychromasia is suggestive of a hemolytic process. White blood cell morphology can also suggest the etiology of the anemia, such as hypersegmented neutrophils in folate or vitamin B_{12} deficiency and basophilic stippling in lead poisoning. The reticulocyte count provides clues to the underlying mechanism of anemia. An elevated reticulocyte count is consistent with hemolysis or blood loss, whereas a reduced or normal reticulocyte count in the setting of anemia suggests a production problem. If hemolysis is evident, a direct antiglobulin test (ie, Coombs test) should be performed to determine if this is an immune-mediated process. Hemoglobin analysis by isoelectric focusing or high-pressure liquid chromatography is used in the diagnosis of sickle cell disease and related disorders and can help distinguish between α- and β-thalassemia traits.

With the complete blood cell count, peripheral blood smear, and reticulocyte count, a focused differential diagnosis can be generated, and more specific testing can be performed. Additional studies specific for individual hemolytic diseases or particular diseases secondary to marrow failure are summarized in Table 98.2.

Imaging Studies

Imaging studies are rarely required in the evaluation of children with anemia. If performed in children with chronic hemolytic disorders, radiography may reveal "hair-on-end" appearance of bones

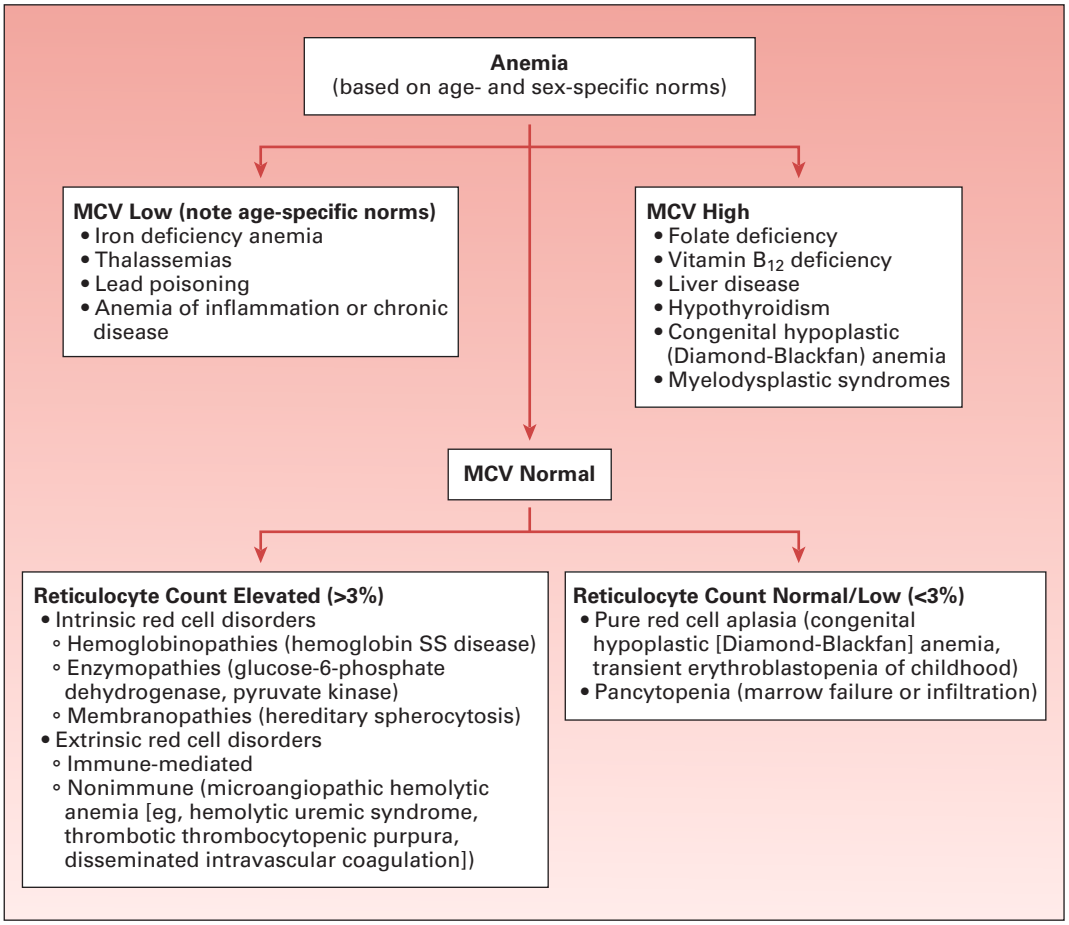

Figure 98.1. Anemia mean corpuscular volume (MCV) classifications.

resulting from increased hematopoiesis. Patients who have anemia associated with lead poisoning may have lead deposition, referred to as "lead lines," in the long bones. Patients with congenital hypoplastic anemia or Fanconi syndrome may have skeletal abnormalities visible on plain radiography.

Management

The treatment of anemia varies depending on the etiology. Nutritional anemias require dietary counseling and nutrient supplementation. With iron deficiency anemia, oral iron supplementation (3–6 mg/kg per day elemental iron divided into 2–3 doses) should generate a brisk reticulocytosis within 7 days, and the hemoglobin should increase by 1.0 g/dL per week thereafter. Therapy should be continued for an additional 6 to 8 weeks after the hemoglobin has normalized to replete iron stores, which can be assessed by monitoring ferritin levels. Dietary education is key to ensure that milk intake is reduced and that iron-rich foods are encouraged. Failure to respond to iron therapy is most commonly the result of noncompliance; however, alternative diagnoses (eg, thalassemia trait), ongoing blood loss, or malabsorption states should also be considered.

Patients with severe thalassemia syndromes (ie, β-thalassemia major) are transfusion-dependent, often requiring transfusions every 3 to 4 weeks to maintain a hemoglobin level ranging from 9 to 10.5 g/dL. With transfusion therapy, progressive iron deposition in tissues occurs, resulting in cardiac, hepatic, and endocrinologic complications, which can be fatal if not prevented. Iron chelation with deferoxamine or deferasirox has improved survival; however, compliance remains an issue. Hematopoietic stem cell transplantation has been performed in patients with severe thalassemias and sickle cell disease.

Depending on the degree of hemolysis and compensation, individuals with congenital hemolytic anemias may require no transfusions, intermittent transfusions to manage anemia during an aplastic crisis, or regular transfusions. Individuals may require folate supplementation and should be monitored for potential complications such as gallstones and aplastic crises. The more severely affected individuals may benefit from splenectomy. Individuals with G6PD deficiency should be counseled on the avoidance of potential triggers of hemolysis.

Two anemia-related conditions—splenic sequestration and severe autoimmune hemolytic anemia—constitute emergencies. Prompt recognition of these conditions is vital if proper treatment is to be initiated. *Splenic sequestration* occurs in infants and young children with sickle cell disease who sequester large volumes of blood within the spleen over a period of hours. This results in rapidly dropping hemoglobin, and the condition clinically resembles anemia because of massive blood loss. The blood pooled in the spleen is not available to the circulation, and affected children are at risk for fatal splenic rupture. Early recognition is essential, and treatment involves emergency volume repletion followed by transfusion or exchange transfusion. Severe autoimmune hemolytic anemia is the second anemia-related emergency. Children with this disorder occasionally present with severe antiglobulin-positive anemia and clinical evidence of rapid hemolysis; their hemoglobin may fall as much as 1 g/dL per hour. Typically, these patients require hospitalization, transfusion, and treatment with high-dose steroids.

The primary treatment of patients with congenital hypoplastic anemia is steroids and RBC transfusions. Most patients (50%–75%) will respond to steroids, and their anemia can be controlled at very low doses. For patients with steroid-refractory anemia, alternative immunosuppressive therapy and RBC transfusions are necessary. Patients with congenital hypoplastic anemia and Fanconi syndrome that is refractory to steroid treatment can be successfully treated with hematopoietic stem cell transplantation.

Previously, hydroxyurea was the only US Food and Drug Administration treatment approved for sickle cell disease. Recently, an oral L-glutamine formulation was approved as a sickle cell disease–modifying medication for patients 5 years of age and older. This approval was based on the results of a phase 3 clinical study, which demonstrated reduction of pain crisis and hospitalizations.

Gene therapy for sickle cell disease is an active field of research, and the first successful case using lentiviral vector for normal β-globin gene delivery was reported in 2017. Even partial expression of normal β-globin provides therapeutic antisickling effect and functional cure, indicating great potential of gene therapy for sickle cell disease.

Prognosis

The prognosis for a child with anemia depends on the underlying cause. The prognosis is excellent for children with anemia caused by nutritional deficiencies that are detected and appropriately managed. Children with transient erythroblastopenia of childhood can expect complete recovery. Most immune-mediated anemias are responsive to therapy; however, if they are associated with an underlying autoimmune disorder, they may have a relapsing course. Children with chronic hemolytic disorders have varying courses depending on the degree of hemolysis. Early diagnosis and intervention through newborn screening for children with sickle cell disease has significantly reduced early mortality for this disease. Children with β-thalassemia major or severe congenital hemolytic anemias are transfusion-dependent and subject to the complications of iron overload, which can be addressed with chelation therapy. Some children with transfusion-dependent congenital hemolytic anemias may be candidates for splenectomy, with normalization of their hemoglobin values postsplenectomy. The prognosis for children with congenital hypoplastic anemia depends on their responsiveness to steroid therapy and need for transfusions. These individuals, along with children with Fanconi syndrome, are also at risk for certain malignancies (eg, acute myeloid leukemia).

When to Refer

Children with anemia caused by chronic inherited or acquired red cell disorders are at risk for complications during the course of their disease and are best served at a center that offers pediatric hematology expertise. Sickle cell disease and severe thalassemias are usually diagnosed by newborn screening programs and are automatically

referred to subspecialists. Any anemia that is complicated by thrombocytopenia or neutropenia also warrants immediate referral to a hematologist.

CASE RESOLUTION

The girl has hereditary spherocytosis. Her history is strongly suggestive of a hereditary hemolytic disorder, and the combination of spherocytes in the peripheral smear, a negative antiglobulin test, and a positive, incubated, osmotic fragility test are diagnostic of the condition. At age 9 years, she undergoes a splenectomy and has no more hemolytic episodes that require transfusions.

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CHAPTER 99

Bleeding Disorders

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CASE STUDY

A 6-year-old girl presents with a several-month history of recurrent epistaxis. Episodes occur every 2 to 3 weeks, with each episode lasting 15 to 20 minutes. Both nares are affected. Her mother also notes that the girl has always bruised easily. On physical examination, several 2- to 3-cm ecchymoses are noted on her lower extremities. Initial laboratory evaluation includes a complete blood cell count, which is normal (platelet count, 300,000/μL); a normal partial thromboplastin time of 30 seconds; and a normal prothrombin time of 12.5 seconds, with an international normalized ratio of 1:1.

Questions

1. What conditions should be considered when easy bruising is the chief presenting symptom?
2. What is the appropriate laboratory evaluation for children with clinical signs of bleeding?
3. What management is appropriate for the most common pediatric bleeding disorders?
4. What are the common medical complications that children with bleeding disorders experience?
5. When is consultation with a hematologist appropriate in a child who bruises easily?

When evaluating a child with bruising or bleeding symptoms, the major challenge for the pediatrician is ascertaining whether the degree of bleeding is appropriate for the hemostatic stress or whether further evaluation for a potential bleeding disorder is warranted. Bruising and bleeding are common childhood occurrences and usually follow minor injury or trauma. In the child with an underlying hemostatic disorder, non-accidental trauma, or both, however, the bruising or bleeding may be more extensive than expected. A thorough medical history and physical examination and an understanding of hemostasis aids in focusing the laboratory evaluation and elucidating the underlying etiology.

Epidemiology

Bleeding disorders may be inherited or acquired. Of the inherited bleeding disorders, von Willebrand disease is the most common, with a reported prevalence of between 1 in 100 and 1 in 1,000. von Willebrand disease is of autosomal inheritance, affecting males and females equally; more females are diagnosed, however, because of the inherent hemostatic challenges that they experience (eg, menses, childbirth). Hemophilia is the most common severe bleeding disorder, affecting approximately 1 in 5,000 males. Approximately 80% of cases are hemophilia A (factor VIII [FVIII] deficiency) and 20% are hemophilia B (factor IX [FIX] deficiency). Hemophilia is inherited in an X-linked fashion, but one-third of newly diagnosed males have no previous family history and represent new mutations. Other inherited coagulation and platelet disorders are rare (Table 99.1).

Acquired abnormalities of coagulation or platelets are much more common than inherited coagulopathies. Acquired abnormalities may be associated with liver disease, renal disease, malignancy, autoimmune or alloimmune disorder, vitamin K deficiency, infection, disseminated intravascular coagulation (DIC), massive transfusion, medication use, and surgery. Immune thrombocytopenic purpura (ITP) is a common acquired childhood bleeding disorder with an incidence of 4 to 8 per 100,000 children per year. Neonatal alloimmune thrombocytopenia occurs in approximately 1 in 1,800 live births. Common acquired bleeding disorders are also listed in Table 99.1.

Clinical Presentation

Bleeding disorders can manifest in various ways depending on the etiology. Inherited bleeding disorders often manifest during infancy or early childhood; mild disorders, however, may go undiagnosed until later in life. In general, disorders of primary hemostasis (eg, von Willebrand disease, platelet disorders, collagen vascular disorders) manifest with superficial, immediate, mucocutaneous bleeding. Characteristic bleeding symptoms include easy bruising, epistaxis, bleeding gums, menorrhagia, postpartum bleeding, and bleeding with dental extractions or surgeries. Disorders of secondary hemostasis, such as hemophilia A or B, often manifest with deep, delayed bleeding, such as hemarthrosis or muscular hematoma.

Acute onset is typical of acquired bleeding disorders, and they often involve abnormalities of primary and secondary hemostasis. Acute onset of bleeding symptoms in a toxic or ill-appearing child is suggestive of a systemic process, such as sepsis, DIC, malignancy, or hepatic or renal dysfunction. A well-appearing child with acute bleeding symptoms is suggestive of ITP, an acquired inhibitor, or a medication-related cause.

Table 99.1. Inherited Versus Acquired Bleeding Disorders

Disorder	*Inherited*	*Acquired*
Coagulation	von Willebrand disease Hemophilia A (FVIII) Hemophilia B (FIX) Hemophilia C (FXI) FII, FV, FVII, FX, or FXIII deficiency Disorders of fibrinogen • Dysfibrinogenemia • Hypofibrinogenemia • Afibrinogenemia Disorders of fibrinolysis • α_2-antiplasmin Plasminogen activator inhibitor-1 deficiency	Vitamin K deficiency Liver disease DIC Massive transfusion syndrome Disorders of fibrinogen (ie, dysfibrinogenemia, hypofibrinogenemia) • Liver disease • Renal disease • Medication-related Disorders associated with malignancy and therapy (ie, asparaginase) Coagulation inhibitors
Platelet	Quantitative • Thrombocytopenia-absent radius syndrome • Amegakaryocytic thrombocytopenia • Fanconi syndrome Qualitative • Glanzmann thrombasthenia • Storage pool disease • Release defects Quantitative/qualitative • Bernard-Soulier syndrome • Wiskott-Aldrich syndrome • Gray platelet syndrome	Quantitative • Increased destruction — Nonimmune-mediated ■ Hemolytic uremic syndrome ■ Thrombotic thrombocytopenic purpura ■ DIC — Immune-mediated ■ Immune thrombocytopenic purpura ■ Evans syndrome ■ Neonatal alloimmune thrombocytopenic purpura ■ Medications • Decreased production — Aplastic anemia — Malignancy infiltrating bone marrow — Medication Qualitative • Medication-related • Liver disease • Uremia • Post-cardiopulmonary bypass surgery

Abbreviations: DIC, disseminated intravascular coagulation; F, factor.

Pathophysiology

After vascular injury, hemostasis is initiated by exposure of flowing blood to subendothelial collagen and tissue factor (TF). The primary phase of hemostasis results in the production of a platelet plug. von Willebrand factor (vWF), a multimeric glycoprotein (GP) of varying size, attaches to exposed subendothelial collagen and binds platelets via the platelet GPIb-V-IX receptors. von Willebrand factor also serves as a carrier protein for FVIII, thereby localizing FVIII to areas of endothelial disruption. After platelets adhere to vWF, they become activated and release their granular contents, produce thromboxane A_2, and express the fibrinogen receptor GPIIb/IIIa. The release of thromboxane A_2 and other granular contents results in local vasoconstriction and activation of additional platelets and their respective GPIIb/IIIa receptors, thereby facilitating platelet aggregation. Fibrinogen binds to all the exposed activated GPIIb/IIIa sites, clumping the platelets together to form a platelet plug. The platelet plug stops local bleeding and provides a phospholipid surface on which the coagulation reactions of secondary hemostasis occur to form a definitive fibrin plug.

Secondary hemostasis is also initiated at the time of endothelial disruption with exposure of TF to circulating blood. Tissue factor binds to factor VIIa (FVIIa), and this complex serves as the key initiator of in vivo hemostasis by activating other TF:FVIIa complexes, as well as FIX and factor X (FX). Once Fx is activated (by FIXa or TF:FVIIa), FXa, along with its cofactor, factor Va, activates prothrombin (ie, factor II) to thrombin (ie, factor IIa). Thrombin cleaves circulating fibrinogen to fibrin monomers that self-polymerize. Factor XIII then stabilizes the fibrin clot by forming cross-links within the clump of fibrin polymers. These coagulation reactions occur on the surface of the platelet plug and, with the generation of cross-linked fibrin, the primary platelet

plug is converted into a definitive fibrin plug that prevents further bleeding. An overview of hemostasis is depicted in Figures 99.1 and 99.2. Deficiencies or impairments in any of these elements can result in abnormal test results or inadequate hemostasis and excessive hemorrhage.

The delicate balance of hemostasis and thrombosis is maintained by inhibitors (eg, protein C, protein S, antithrombin, TF pathway inhibitor) at each step of the coagulation pathway. These natural anticoagulants prevent excessive thrombus formation. Fibrinolysis is mediated by plasmin, which cleaves fibrinogen and fibrin within a thrombus, which enables restoration of vessel patency following hemostasis. Plasmin is activated by tissue plasminogen activator and urokinase. Fibrinolysis is kept in check by plasminogen activator inhibitor-1 (PAI-1), which inactivates tissue plasminogen activator, and α_2-antiplasmin, which inactivates plasmin. Any defect in the fibrinolytic system that results in increased fibrinolysis can cause excessive bleeding.

Differential Diagnosis

In developing the differential diagnosis for a child with bleeding symptoms, it is important to obtain a thorough bleeding history and perform a thorough physical examination. The age, bleeding pattern, duration of symptoms, family history, and overall clinical status of the child may help narrow the spectrum of possibilities.

Child With Chronic History of Mucocutaneous Bleeding

In a child who presents with a history of easy bruising, epistaxis, or menorrhagia, the primary differential diagnosis includes von Willebrand disease, platelet disorders, and collagen vascular disorders (ie, disorders of primary hemostasis). von Willebrand disease is caused by a quantitative or qualitative defect of vWF. von Willebrand factor plays an important role in both primary hemostasis, by mediating platelet adhesion at sites of vascular injury and secondary hemostasis, by stabilizing FVIII in plasma. von Willebrand disease is one of autosomal inheritance and has 3 types: partial quantitative deficiency of vWF (type 1); qualitative abnormalities of vWF (types 2A, 2B, 2C, and 2D); and the most severe form—complete deficiency of vWF (type 3)—which is caused by homozygous or compound heterozygous mutation and is inherited in autosomal-recessive fashion. Type 1 is the most common form, accounting for 70% to 80% of cases. Bleeding symptoms tend to be mild and are characterized by easy bruising, epistaxis, menorrhagia, and prolonged oozing after minor or major surgeries. Only the most severely affected patients (ie, with type 3 disease) and with very low FVIII levels experience soft tissue bleeding and hemarthroses similar to that of an individual with moderate or severe hemophilia.

Qualitative platelet disorders also manifest with mucocutaneous bleeding, often during infancy. In *Bernard-Soulier syndrome*, platelets lack a functional GPIb-V-IX receptor complex on the platelet

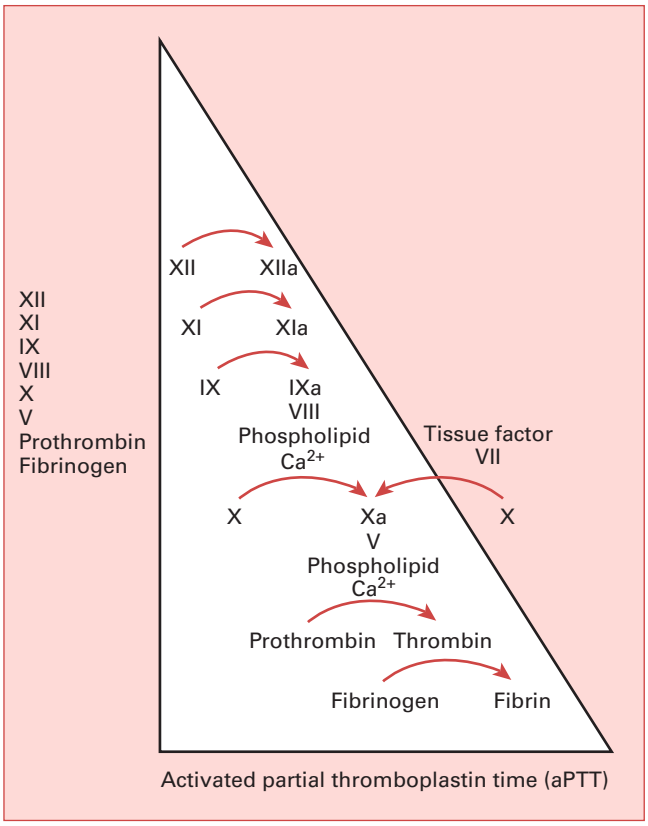

Figure 99.1. Intrinsic pathway reflected by activated partial thromboplastin time. The roman numerals represent factors.

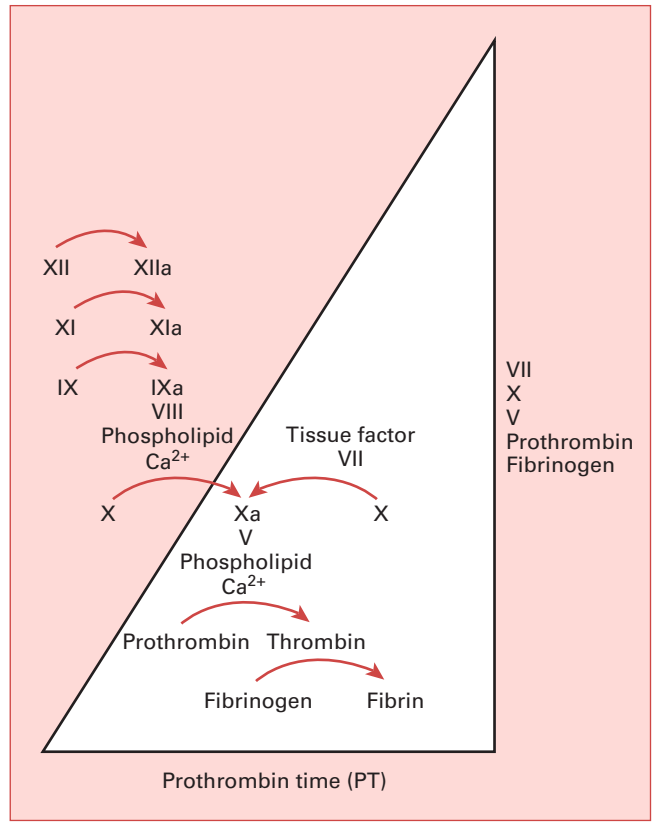

Figure 99.2. Coagulation pathway. Extrinsic pathway reflected by prothrombin time. The roman numerals represent factors.

surface, resulting in defective platelet adhesion to vWF at sites of vascular injury. This autosomal-recessive disorder is usually seen in the presence of consanguinity. The platelets tend to be large on peripheral blood smear, and thrombocytopenia may be present. *Glanzmann thrombasthenia* is characterized by an absence or defect in the platelet membrane GPIIb/IIIa receptor, the main fibrinogen receptor on the platelet surface that enables platelet aggregation. Inheritance is autosomal-recessive, and the condition is most common in the presence of consanguinity. Other qualitative platelet disorders, such as storage pool disease and platelet release defects, also can manifest in a similar manner.

Collagen-vascular disorders, such as Marfan syndrome and Ehlers-Danlos syndrome, may manifest with bruising and bleeding symptoms. This increased bleeding diathesis is caused by an easy disruption of the integrity of the vascular endothelium.

Other rare coagulation disorders to consider in a child with recurrent bleeding symptoms include deficiencies of factor XI, factor XIII (FXIII), PAI-1, and α_2-antiplasmin. *Factor XI deficiency* (ie, *hemophilia C*) is a rare bleeding disorder with a high prevalence in the Ashkenazi Jewish population. It differs from other types of hemophilia in that inheritance is autosomal and symptoms tend to be milder. Bleeding episodes typically occur in response to trauma or surgery; these episodes do not include the deep tissue or intra-articular bleeds characteristic of FVIII and FIX deficiency. *Factor XIII deficiency* is characterized by delayed or prolonged bleeding because the clots formed are friable, resulting from the lack of cross-linkage of fibrin monomers by FXIII. The inheritance is autosomal-dominant, and in the homozygous state it usually manifests in infancy with umbilical cord bleeding or delayed separation, as well as intracranial hemorrhage. Heterozygous individuals may present later in life with delayed or prolonged bleeding after trauma or surgery as well as poor wound healing. Disorders of fibrinolysis (eg, deficiency of PAI-1 or α_2-antiplasmin) also may manifest with prolonged bleeding after trauma.

Child With a History of Deep, Delayed Bleeding

Deep tissue and intra-articular bleeding is the hallmark bleeding pattern of hemophilia. Differential diagnosis for a child who presents with this type of bleeding is hemophilia A (ie, FVIII deficiency) or B (ie, FIX deficiency), FVII deficiency, and type 3 von Willebrand disease. Clinically, hemophilia is classified according to the factor level: less than 1% factor activity (severe), 1% to 5% (moderate), and greater than 5% (mild). The factor level correlates with the bleeding tendency. Males with severe hemophilia can have "spontaneous" bleeds or bleeding with minimal trauma. Males with moderate or mild hemophilia bleed with more significant trauma. The bleeding pattern of hemophilia varies as the child grows. Infants may present with a cephalohematoma or intracranial hemorrhage, particularly if the delivery was complicated by the use of forceps or vacuum extraction. Bleeding with circumcision, heel sticks, or blood draws may also occur. As the infant starts crawling, bruises and soft tissue hematomas on the lower extremities become common. As the toddler becomes upright, the first hemarthroses can occur, typically involving the ankle. The older child incurs hemarthroses primarily of the knees and elbows.

Factor VII deficiency is rare; however, it can manifest with a bleeding pattern similar to that of hemophilia A or B. The patient with type 3 von Willebrand disease, which is characterized by an absence of vWF (the carrier protein for FVIII), may have FVIII levels as low as an individual with severe or moderate hemophilia A. In addition to the characteristic mucocutaneous bleeding that occurs with von Willebrand disease, these individuals also experience deep tissue and intra-articular bleeding.

Well-Appearing Child With Acute Onset of Bleeding Symptoms

Acute onset of bleeding symptoms is consistent with an acquired abnormality of hemostasis. *Acute ITP* is a common acquired bleeding disorder of childhood that is caused by the development of autoantibodies directed against the patient's platelets. These autoantibodies, which cross-react with platelet surface antigens, are thought to develop in response to infection. Typically, a healthy child (usually between ages 2 and 4 years) presents with abrupt onset of bleeding symptoms, diffuse petechiae and bruising, and occasionally, "wet" bleeding (eg, epistaxis, gum bleeding, gastrointestinal [GI] bleeding). Often a history exists of a viral illness or recent immunization. The complete blood cell count (CBC) reveals isolated thrombocytopenia, and large platelets are seen on peripheral blood smear, which is indicative of active marrow and production of young platelets. In approximately 80% of cases, ITP is an acute, self-limited process that resolves within 6 months of diagnosis with or without therapy. *Chronic ITP* exists when the thrombocytopenia persists longer than 6 months. Although it is impossible to predict at diagnosis whether a patient will progress to chronic ITP, certain presenting features are associated with increased risk for chronicity. These include older age at presentation (>10 years), female sex, existing autoimmune disease, and insidious onset of symptoms. In most cases of chronic ITP, the platelet count ranges between 40,000 and 80,000/μL, and bleeding symptoms are minimal.

Acquired coagulation inhibitors are rare in children who do not have an underlying coagulation disorder; however, they can occur in the setting of malignancy or infection or postoperatively. Acquired FVIII deficiency resulting from FVIII inhibitor occurs primarily in the adult population but has been reported in children. Acute onset of severe bleeding symptoms is the common presentation. Antiphospholipid antibodies can cause prolonged partial thromboplastin time (PTT) or prothrombin time (PT); however, these antibodies are not associated with bleeding and are typically transient after a viral illness. If the antiphospholipid antibody is specifically directed against prothrombin, prothrombin levels will be low and the prothrombin time elevated. In this situation, if bleeding occurs it is usually mild and intervention is unnecessary.

Acquired abnormalities of coagulation or platelet function also can occur in association with certain medications. Aspirin and nonsteroidal anti-inflammatory drugs are common medications that

affect platelet function. Warfarin, a vitamin K antagonist, is commonly used as an anticoagulant. One percent to 3% of patients on therapeutic warfarin experience bleeding complications. Chronic antibiotic use can result in vitamin K deficiency and depletion of the vitamin K-dependent factors (ie, II, VII, IX, X).

Ill-Appearing Child With Acute Onset of Bleeding Symptoms

Acute onset of bleeding in an ill-appearing child is suggestive of an acquired systemic process. *Disseminated intravascular coagulation* is a consumptive coagulopathy that can occur secondary to several disorders, including sepsis, trauma, and malignancy. Disseminated intravascular coagulation occurs as a result of endothelial disruption and initiation of abnormal coagulation (ie, fibrin deposition along with depletion of multiple clotting factors, inhibitor proteins, and platelets).

Because the liver is the primary site of synthesis for most of the coagulation factors, liver dysfunction caused by any illness can result in an imbalance in the hemostatic system. Additionally, thrombocytopenia may be present in the patient with chronic liver disease because of portal hypertension and associated splenomegaly with sequestration. Causes of the depletion of vitamin K–dependent factors, such as obstructive jaundice, malabsorptive states (eg, cystic fibrosis), parenchymal liver disease, and chronic antibiotic use, can also predispose the patient to bleeding.

Renal disease with uremia impairs platelet function and may manifest with bleeding symptoms as well. A malignancy that infiltrates the bone marrow, such as leukemia, lymphoma, or neuroblastoma, can cause thrombocytopenia and resultant platelet bleeding. Acquired von Willebrand disease can occur in the patient with Wilms tumor and manifest with mucocutaneous bleeding. Bone marrow failure syndromes, such as aplastic anemia and Fanconi syndrome, also may manifest with thrombocytopenia and associated bleeding.

The Newborn or Infant With Bleeding Symptoms

The newborn or infant who presents with bleeding symptoms may have a congenital bleeding disorder or an acquired condition. Inherited coagulation factor deficiencies (FVII, FVIII, FIX, FXI, FXIII, type 3 von Willebrand disease) and qualitative platelet disorders may manifest in the newborn period with intracranial hemorrhage or cephalohematoma, bleeding with heel sticks or blood draws, umbilical cord bleeding, and bleeding with circumcision. Congenital thrombocytopenia usually manifests within the first year after birth and is associated with other syndromic features. Thrombocytopenia-absent radius syndrome is an autosomal-recessive condition that typically is recognized in the newborn period and is characterized by thrombocytopenia, skeletal anomalies (most commonly radial agenesis), and renal and cardiac abnormalities. Other types of congenital thrombocytopenia include amegakaryocytic thrombocytopenia; Fanconi syndrome (with associated skeletal anomalies); and Wiskott-Aldrich syndrome, which is characterized by eczema, frequent infections, and small platelets.

Neonatal alloimmune thrombocytopenia (NAIT) is a rare condition in which a newborn inherits platelet antigens from the father that are different from those of the mother. The mother becomes alloimmunized to the fetal platelet antigens during pregnancy, similar to the process of erythrocyte alloimmunization resulting from Rh incompatibility. The maternal immunoglobulin G alloantibodies cross the placenta and destroy fetal and newborn platelets, resulting in transient but severe thrombocytopenia in the newborn. Antibodies against the human platelet antigen-1a are responsible for 80% of cases of NAIT among whites. Thrombocytopenia in the newborn or infant can last several weeks, until the maternal antibody is cleared. Unlike Rh alloimmunization, NAIT can occur in the first pregnancy. The risk of intracranial hemorrhage is significant, with a reported incidence of up to 20% in some studies, and it can occur in utero. Neonatal thrombocytopenia also can occur as a result of maternal ITP, with maternal transfer of antibody. Bleeding tends to be mild in this setting, and intracranial hemorrhage is rare. The thrombocytopenia resolves after several weeks. Acquired thrombocytopenia most often occurs in the setting of an ill newborn or infant with sepsis, congenital infection (eg, *Toxoplasma,* rubella, cytomegalovirus, HIV), necrotizing enterocolitis, respiratory distress syndrome, asphyxia, or congenital heart disease. Drug-associated thrombocytopenia also may occur in the hospitalized newborn or infant.

Vitamin K deficiency in the neonate has 3 different presentations. *Classic hemorrhagic disease of the newborn* manifests between days 2 and 7 of age and is the result of immature neonatal liver and impaired clotting factor synthesis, inadequate vitamin K intake, and sterile neonatal gut. With the advent of vitamin K prophylaxis at birth, this form of vitamin K deficiency is rare. *Early hemorrhagic disease of the newborn* manifests in the first 24 hours after birth and is caused by maternal medications that affect vitamin K metabolism (eg, anticonvulsants). *Late vitamin K deficiency* occurs after 1 week of age and is associated with several conditions in which vitamin K stores may be low, such as inadequate intake in breastfed neonates and infants, impaired absorption in neonates and infants with chronic diarrhea, antibiotic use, cystic fibrosis, and other GI disorders. Bleeding symptoms associated with vitamin K deficiency can be severe, with a significant incidence of GI, deep tissue, and intracranial hemorrhage.

Exposures to the superwarfarin vitamin K antagonists found in rat poisons are relatively common in children but are usually asymptomatic, because it is necessary to ingest a large quantity of rat poison to induce significant coagulopathy. However, this intoxication should be considered in patients presenting with extreme coagulopathy and unexplained elevation of PT and activated PTT (aPTT) secondary to depletion of vitamin K–dependent factors.

Evaluation

History

A thorough bleeding history and physical examination should enable the pediatrician to determine the likelihood of an underlying bleeding disorder. The pattern of bleeding, timing of the symptoms (acute

or chronic), overall health of the child, and family history are important in helping determine the underlying etiology. Box 99.1 lists the pertinent questions to ask when obtaining a bleeding history.

Bruises are common in childhood. Normal bruising that occurs in an active child must be differentiated from pathologic bruising resulting from a possible bleeding disorder or non-accidental trauma. Bruises over exposed bony prominences, such as the anterior tibia or the knee, are common. Bruises of a size inconsistent with the degree of reported trauma, and bruises in unexposed or unusual areas (ie, back, chest, shoulders, upper arms), should alert the pediatrician to a possible bleeding disorder or non-accidental trauma. Linear or geometric bruises are concerning for non-accidental trauma. Epistaxis, another common occurrence, typically is caused by digital trauma or allergic rhinitis. However, epistaxis that is unrelieved by 15 minutes of appropriately applied pressure or epistaxis requiring packing, cautery, or transfusion is highly suggestive of a bleeding disorder. *Menorrhagia*, that is, menstrual flow longer than 7 days, and a history of frequently blood-stained clothes or iron deficiency anemia in the adolescent female are concerning. Persistent or recurrent bleeding with dental extractions (beyond the day of the procedure) or with surgeries also merits a closer evaluation. However, if a child has undergone previous dental extractions or surgeries without bleeding complications, an underlying bleeding disorder is unlikely. A history of deep muscle bleeding or unexplained hemarthroses is suggestive of an inherited factor deficiency.

Box 99.1. What to Ask

Bleeding History

- Does the child have a history of bleeding, or is the child presenting for incidentally discovered abnormal tests (eg, prolonged prothrombin time/activated partial thromboplastin time)?
- Is the bleeding acute or chronic?
  - For acute-onset bleeding
    - What type bleeding is the child experiencing?
    - Is the child well- or toxic-appearing?
    - Is there a history of recent illness?
    - Is the child taking any medications?
    - Does the child have any medical problems?
  - For history of chronic bleeding
    - What type bleeding is the child experiencing?
    - How long has the child been experiencing the bleeding episodes?
- Can you characterize any bruising (eg, location, size, palpable hematoma)?
- If the child has experienced epistaxis (ie, nosebleed), can you indicate duration of bleeding as well as any history of packing, cauterization, or transfusion?
- Has the child experienced bleeding with vaccinations, injections, or minor cuts?
- Has the child experienced bleeding with dental extractions and/or surgeries?
- Can you characterize the child's menses with regard to total number of days of bleeding, whether leaking occurs, whether there is alteration of activities during menses, whether iron deficiency has been diagnosed, whether oral contraceptives are used, and whether the child has a history of transfusion?
- What medications, if any, does the child take?
- What is the obstetric and gynecologic history of female relatives?

Physical Examination

Depending on the underlying bleeding disorder and the time of presentation, the physical examination may be completely normal. In the patient with active bleeding, physical signs may include petechiae, ecchymoses, mucosal bleeding (ie, nasal, oral, vaginal), hematuria, swollen joints (ie, hemarthrosis), or limited range of motion. Children with bleeding associated with an acquired disorder such as infection, malignancy, autoimmunity, or liver or renal dysfunction may have physical signs specific to the underlying illness. Children with bleeding associated with a genetic disorder may have a normal examination or congenital anomalies associated with a particular syndrome.

Laboratory Tests

The extent of laboratory evaluation is dependent on the bleeding history and clinical presentation. Initial laboratory studies for a potential bleeding disorder should include a CBC with a peripheral blood smear, a PT, and an aPTT.

The CBC is useful in providing a platelet count for identification of suspected thrombocytopenia. Additionally, abnormalities in the white blood cell count or red cell indices can provide clues to the underlying process. Microcytic anemia consistent with iron deficiency is suggestive of chronic blood loss and raises suspicion for an underlying bleeding disorder. Pancytopenia is suggestive of an underlying bone marrow failure syndrome or a possible malignancy, such as leukemia. Review of the peripheral blood smear can confirm the presence of thrombocytopenia as well as allow for an assessment of platelet, white blood cell, and red blood cell morphology.

The PT reflects the extrinsic and common clotting pathway, and the aPTT reflects the intrinsic and common pathway of the clotting cascade. In the patient with a prolonged PT or PTT, a 1:1 mixing study should be done to determine whether the prolongation is caused by a factor deficiency or the presence of an inhibitor. *Bleeding time* assesses primary hemostasis (ie, platelet function, vWF, vascular integrity); however, it is rarely performed in pediatric patients because of the unreliability and difficulty of performing this test in children. The *platelet function assay* is a screening test of platelet function used to measure platelet adhesion and aggregation (ie, primary hemostasis).

A stepwise approach to more specific testing is dictated by the clinical presentation and screening test results and is best performed with the consultation of a pediatric hematologist. When an abnormality of primary hemostasis is suspected, the initial evaluation should focus on von Willebrand disease because it is the most common disorder. A vWF panel, which includes vWF antigen, ristocetin cofactor activity (a functional measure of vWF), FVIII activity, and a vWF multimer analysis, should be performed. Many factors, such as stress, inflammation, hormones, exercise, and oral contraceptives, may transiently increase vWF levels, and normal results

are frequently returned in patients with type 1 von Willebrand disease. Repeat testing is often necessary to make the diagnosis and should be pursued if suspicion is high for von Willebrand disease. For the patient with hemophilia or any other suspected factor deficiency, a specific coagulation factor assay must be performed. For the patient with suspected qualitative platelet disorder, either *platelet aggregation studies*, which measure the degree and pattern of platelet aggregation to various agonists, or *flow cytometry*, which measures the platelet surface GP expression, can be performed. Additional studies, such as fibrinogen level, D-dimer assay, fibrin degradation products, thrombin time, factor inhibitor assay, autoimmune studies, liver function tests, serum creatinine test, or blood urea nitrogen test, may be indicated on an individualized basis. Table 99.2 lists the major screening tests for hemostasis.

Imaging Studies

In general, imaging studies are not indicated. In patients with thrombocytopenia, radiographs of the upper extremities may be obtained to rule out Fanconi syndrome and thrombocytopenia-absent radius syndrome. Computed tomography of the head should be considered if intracranial hemorrhage is suspected. In patients with hemophilia, computed tomography of the iliopsoas muscle is indicated if bleeding into the muscle is suspected; however, appropriate factor replacement is a priority over any imaging study.

Management

The management of bleeding disorders is dependent on the underlying abnormality. However, general supportive measures, such as local pressure for bleeding, avoidance of blood draws, and avoidance of medications that affect the function of platelets or hemostasis, are applicable to most clinical scenarios of bleeding.

Treatment of the patient with von Willebrand disease is dependent on the subtype and severity of bleeding symptoms. For mild bleeding symptoms, supportive measures alone may be sufficient, such as applying appropriate pressure for epistaxis, ice pack for bruises, and avoidance of antiplatelet medications. For patients with type 1 von Willebrand disease, desmopressin (eg, synthetic vasopressin) can be used, either as a concentrated nasal spray or intravenously. Desmopressin stimulates endothelial release of vWF and can increase levels 2- to 3-fold. For type 3 and most cases of type 2 von Willebrand disease, replacement therapy with FVIII concentrates containing vWF is necessary for management of significant bleeding episodes. Antifibrinolytic agents, such as aminocaproic acid, are quite effective in the management of mucosal bleeding and can be used alone for mild cases or in conjunction with desmopressin or FVIII/vWF concentrates in more severe episodes of bleeding. For females with menorrhagia, a trial of oral contraceptives is reasonable, because estrogen can increase vWF levels. This response is variable, however, and if it is not effective, use of aminocaproic acid and nasal desmopressin may be necessary.

For most qualitative platelet disorders, management is supportive. Mild bleeding episodes can be managed nonspecifically with antifibrinolytic agents or desmopressin. Platelet transfusions should be reserved for life-threatening bleeds and otherwise avoided because of the risk for developing antibodies.

The management of acute ITP consists of family education, supportive measures, and, in select cases, pharmacologic therapies. The use of pharmacologic therapies in the management of acute ITP remains controversial. In the natural course of acute ITP, the platelet count rises within 1 to 3 weeks of presentation. The rationale for initiating pharmacologic therapies is the theoretical prevention of intracranial hemorrhage; however, the incidence of this complication

Table 99.2. Laboratory Evaluation for Hemostasis

Laboratory Test	*Measured Hemostatic Function*
Complete blood cell count	Platelet count.
Peripheral blood smear	Platelet morphology.
aPTT	Factors I, II, V, VIII, IX, XI, XII (intrinsic and common pathway).
PT	Factors I, II, V, VII, X (extrinsic and common pathway).
aPTT and PT mixing studies	Performed in the patient with prolonged aPTT/PT. Patient plasma and normal plasma is mixed 1:1, and the aPTT/PT is repeated. If aPTT/PT corrects, a factor deficiency exists; if not, an inhibitor exists.
Bleeding time[a]	Primary hemostasis (platelets, vWF, endothelial integrity).
Platelet function assay-100 screen	Primary hemostasis (platelets, vWF).
Thrombin time	Fibrinogen.
vWF panel	vWF antigen (amount of vWF), ristocetin cofactor activity (function of vWF), factor VIII activity, vWF multimer analysis (distribution of multimers).
Coagulation factor assays	Specific factor activity.
Platelet aggregation studies	Platelet function. Platelets are exposed to agonists; the degree of aggregation and pattern of the response is unique to various qualitative platelet disorders.

Abbreviations: aPTT, activated partial thromboplastin time; PT, prothrombin time; vWF, von Willebrand factor.

[a] Not recommended in pediatric patients.

is less than 0.5%, and there are no data which confirm that any of the currently available therapies actually prevent this complication. As opposed to waiting, the platelet count increases more rapidly with pharmacologic intervention and a significant bleeding complication may be prevented. In those at risk for persistent ITP, the use of pharmacologic intervention will not reduce the likelihood of developing chronic ITP. The decision to treat must be individualized, taking into consideration the child's age, bleeding symptoms, and activity level, as well as the parental anxiety level. Treatment options include observation without medical therapy, corticosteroids, intravenous gamma globulin, and anti-D immunoglobulin. Anti-D immunoglobulin can be used only in patients who are Rh positive. In all cases, parents should be instructed to avoid the use of aspirin, ibuprofen, and other antiplatelet medications; avoid intramuscular injections; and postpone immunizations and allergic desensitization injections that may exacerbate the degree of thrombocytopenia. Physical activity should be limited, with specific instruction to avoid activities that may cause head injury. Parents also should be educated about the signs and symptoms of an intracranial hemorrhage and given instructions on what to do in the event of an emergency. Therapeutic options for chronic ITP include observation without therapy, corticosteroids, regular infusions of intravenous immune globulin (IVIG) or anti-D immunoglobulin (for Rh-positive patients), immunosuppressive agents, rituximab, and laparoscopic splenectomy. Rituximab is a chimeric monoclonal antibody directed against CD20 (which is found primarily on the surface of B cells) and has been shown to be effective in managing chronic ITP and other autoimmune conditions. Management of acute bleeding in NAIT includes transfusion of maternal washed platelets and IVIG. If maternal washed platelets are not available, random platelets, preferably crossmatched or negative for human platelet antigen-1a, can be used along with IVIG.

Prevention and early management of bleeding episodes, family education, and good well-child care are important in providing comprehensive hemophilia care. The current standard of care for patients with severe hemophilia is prophylaxis, intravenous factor replacement therapy on a regular schedule, whether every other day, 3 times a week, or twice a week depending on the type of hemophilia, to prevent bleeding episodes. Prophylaxis is usually initiated during the first few years of age. A subcutaneous central venous catheter is inserted for this purpose and, as the child grows, the parents, and eventually the child, are taught how to administer factor by peripheral infusion. Prompt treatment of acute bleeding episodes is essential to prevent long-term complications. In 30% of patients with hemophilia A and 2% to 3% of patients with hemophilia B, an inhibitor to the respective factor can develop. In the presence of an inhibitor, acute bleeding episodes must be managed with bypassing agents, such as prothrombin concentrates or recombinant FVIIa. In the long-term, immune tolerance is attempted by exposing the child to high doses of factor on a daily basis in an attempt to eradicate the inhibitor. Several immune tolerance regimens have been used, with varying success.

More recent efforts in the management of hemophilia have been focused on the development of recombinant factor products with extended half-lives, which requires fewer injections for disease control. A major international study demonstrated that treatment with plasma-derived FVIII is associated with a lower incidence of inhibitors compared with recombinant FVIII. Novel approaches for patients with inhibitors include non-factor bypass agents (eg, anti-tissue-factor pathway inhibitor) or the bispecific antibody emicizumab, which bridges FIX and FX in lieu of replacing FVIII in hemophilia A when inhibitors are present.

Acquired causes of coagulation or platelet abnormalities can be managed supportively or by replacing the deficiency or removing the offending causative agent. Children with DIC may be given fresh frozen plasma, cryoprecipitate, and platelets as needed while the underlying etiology of the DIC is treated. In children in whom vitamin K deficiency is the suspected cause of bleeding, 1 dose of vitamin K should correct the coagulopathy within 12 to 36 hours. Depending on the underlying cause of vitamin K deficiency, regular replacement may be required, as during prolonged antibiotic therapy. Clinically important bleeding in children who have ingested superwarfarin rodenticide may necessitate GI decontamination in addition to administrations of fresh frozen plasma and high-dose vitamin K.

Prognosis

Most patients with inherited bleeding disorders have an excellent prognosis if the diagnosis is made in a timely fashion and appropriate intervention is initiated.

Patients with von Willebrand disease usually have mild bleeding symptoms and, with appropriate education and intervention, have an excellent prognosis. Patients with hemophilia also have an excellent prognosis with early diagnosis, family education, prophylaxis, and early treatment of bleeds. With the advent of prophylaxis, the severe hemophilic arthropathy that plagued prior generations of males with hemophilia has been largely averted or minimized. In addition, the use of recombinant factor products and highly purified plasma-derived products in the pediatric population has largely eliminated the risk for viral transmission. Acute ITP resolves spontaneously by 6 months following diagnosis in 80% of cases, regardless of pharmacologic intervention, and the risk for significant hemorrhage is exceedingly low. Most cases of chronic ITP resolve with time, and significant bleeding complications do not usually occur.

When to Refer

Most cases of elevated PT/PTT are the result of nonspecific inhibitors that are transient and do not cause bleeding. Generally, subspecialty referral is not required. Often routine ITP can be managed by a primary pediatrician; however, if the diagnosis is in question, a hematologist should be consulted. Patients with hemophilia and other severe bleeding disorders are usually diagnosed in infancy and require close follow-up with a pediatric hematologist in the setting of a comprehensive hemophilia treatment center.

CASE RESOLUTION

A vWF panel was performed and revealed a vWF antigen of 20%, ristocetin cofactor activity of 30%, FVIII activity of 40%, and a normal multimer analysis. The girl was diagnosed with type 1 von Willebrand disease. A desmopressin challenge was performed in the clinic, and she had an excellent response. She was prescribed nasal desmopressin and aminocaproic acid for use in significant bleeding episodes.

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CHAPTER 100

Lymphadenopathy

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CASE STUDY

A 12-year-old girl is brought to the office with swelling of the anterior cervical nodes, which has persisted for 2 weeks. Intermittent fever with temperatures as high as 38.3°C (101°F) and decreased appetite have been associated with the condition. On physical examination, her temperature is 38.0°C (100.4°F) and her other vital signs are normal. Three to 4 nontender nodes 1 to 2 cm in diameter are present bilaterally. The remainder of the examination is normal.

Questions

1. When is lymphadenopathy of medical concern?
2. What are the clinical features of childhood diseases that present as cervical lymphadenopathy?
3. What are the diagnostic approaches to the evaluation of children with lymphadenopathy?
4. What is an appropriate therapeutic approach to cervical lymphadenopathy in children?

Lymphadenopathy is among the most common clinical problems encountered in pediatrics. Palpable lymph nodes are a source of anxiety for parents, often prompting a visit to the pediatrician for evaluation. Although most cases are caused by a benign, self-limited infectious process, lymphadenopathy may also signal a serious underlying systemic illness. It is important for the pediatrician to make this distinction so that appropriate diagnostic and therapeutic measures can be initiated when necessary.

Epidemiology

Lymphadenopathy occurs frequently in childhood, and even healthy children may have palpable lymph nodes in the anterior cervical, inguinal, and axillary regions. Localized lymphadenopathy is mainly caused by an infectious etiology, whereas generalized lymphadenopathy occurs with systemic illnesses, such as systemic infections (ie, viral, bacterial, protozoal, fungal), autoimmune disorders, storage disorders, and malignancies.

Clinical Presentation

Lymphadenopathy may be localized or generalized on presentation. *Localized* or *regional lymphadenopathy* refers to enlargement of lymph nodes within contiguous regions, whereas *generalized lymphadenopathy* involves more than 2 noncontiguous lymph node groups (Box 100.1). Infection is the most frequent cause of localized lymphadenopathy in children. The anterior cervical lymph node region is the most commonly involved area because it is affected by upper respiratory infections (URIs), which occur frequently in childhood. Bilateral cervical lymphadenopathy often occurs in viral and bacterial URIs, and the nodes tend to be soft, mobile, and nontender. Viruses such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) can present with prominent posterior cervical lymphadenopathy as well as generalized adenopathy and occasionally hepatosplenomegaly. Direct bacterial invasion of lymph nodes produces lymphadenitis, which typically is unilateral, tender, erythematous, and fluctuant. Subacute or chronic lymphadenopathy may be caused by atypical mycobacterial infections, tuberculosis, cat-scratch disease, EBV, CMV, toxoplasmosis, coccidioidomycosis, or HIV. Generalized lymphadenopathy is concerning for an underlying systemic illness (ie, infection, autoimmune process, storage disease, malignancy). Lymphadenopathy resulting from malignancy typically is characterized by fixed, firm, nontender lymph nodes in the setting of other signs and symptoms, such as fever, pallor, night sweats, and weight loss.

Pathophysiology

Lymph nodes are an integral part of the immune system in which phagocytic cells filter both microorganisms and particulate matter and antigens are presented, thereby provoking a cellular or humoral mediated lymphocyte response. Lymph nodes

Box 100.1. Diagnosis of Lymphadenopathy in Children

- Enlarged lymph nodes
- Fever
- Tenderness or warmth over the lymph nodes (signs of inflammation [ie, lymphadenitis])
- Antecedent infection (eg, pharyngitis, upper respiratory infection, otitis media, skin and soft tissue infections)
- Pallor
- Weight loss
- Bone pain
- Night sweats

Table 100.1. Lymph Node Drainage Patterns

Group	*Drainage Pattern*
Occipital	Posterior scalp
Preauricular	Superficial orbital and periorbital tissue, temporal scalp
Submental/ submandibular	Mouth
Cervical	Mouth, pharynx, ear, parotid gland, deep structures of neck (ie, thyroid, larynx, trachea, upper esophagus)
Supraclavicular	Head, neck, arms, lungs, mediastinum, and abdomen
Mediastinal	Lungs, heart, thymus, esophagus
Axillary	Chest wall, breast, upper extremity
Abdominal	Abdominal organs, pelvis, lower extremities
Iliac and inguinal	Lower extremities, genitalia, buttocks, pelvis

are distributed in groups throughout the body and drain specific regions (ie, head, neck, axilla, mediastinum, abdomen, extremities) (Table 100.1). Enlargement of a lymph node may be caused by proliferation of lymphocytes intrinsic to the lymph node (as a physiologic immune response or a malignant transformation) or infiltration by either pathogens or extrinsic inflammatory or metastatic malignant cells.

Differential Diagnosis

The duration and extent of lymphadenopathy, that is, localized versus generalized; characteristics of the lymph nodes; and presence of associated symptoms help focus the differential diagnosis. A list of common causes of lymphadenopathy in children is provided in Table 100.2.

Localized lymphadenopathy is most often caused by an infectious etiology. Acute bilateral cervical lymphadenopathy is most frequently caused by viral URIs (ie, respiratory syncytial virus, adenovirus, parainfluenza and influenza viruses) or EBV and CMV, which can also cause generalized adenopathy. Bacterial pharyngitis (most commonly *Streptococcus* species) and oral infections or dental abscesses can present with cervical adenopathy. Unilateral lymphadenitis is most often caused by *Staphylococcus aureus,* followed by *Streptococcus pyogenes,* anaerobes, and other species. When the condition appears subacute, the following etiologies should be considered: cat-scratch disease, tuberculosis (ie, scrofula), atypical mycobacteria, toxoplasmosis, tularemia, and, less commonly, histoplasmosis, brucellosis, and syphilis. Cervical lymphadenopathy can also occur with Kawasaki disease, with high fever (5 days' duration); redness, swelling, and desquamation of extremities; nonpurulent conjunctivitis; rash; and swollen lips and tongue.

Generalized lymphadenopathy may be caused by systemic infections (eg, EBV, CMV, HIV, toxoplasmosis), autoimmune disorders (eg, juvenile idiopathic arthritis, systemic lupus erythematosus), storage disorders (eg, Niemann disease, Gaucher disease), histiocytic disorders (eg, Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis), drug reactions (eg, phenytoin), or malignancies. Malignancies include leukemia and lymphoma (Hodgkin and non-Hodgkin) as well as solid tumors that can metastasize to lymph nodes (eg, neuroblastoma, rhabdomyosarcoma). With neoplastic infiltration, enlarged nodes are generally nontender, firm, rubbery, and immobile. In Hodgkin disease, the nodes enlarge sequentially, with involvement spreading from 1 chain to the next. Supraclavicular or epitrochlear adenopathy is strongly suggestive of malignancy.

Several head and neck lesions that occur in the pediatric population are often confused with cervical lymphadenopathy. These lesions include cystic hygromas, branchial cleft cysts, thyroglossal duct cysts, and epidermoid cysts. These are congenital malformations that often present as a neck mass in the young child and can easily be mistaken for a lymph node, particularly if infected (see Chapter 94).

Evaluation

History

A thorough history and review of symptoms is essential in determining the underlying etiology of lymphadenopathy in children. Inquiries should be made about the duration of the lymphadenopathy, rate of nodal enlargement, and occurrence of associated fever and other constitutional symptoms, such as bone pain, weight loss, fever, and night sweats. Recent illnesses or infections, insect or animal bites, and local trauma should be determined. A history of distant travel, recent emigration from countries with endemic tuberculosis (eg, Mexico, Central America, Southeast Asia), recent travel to areas with endemic histoplasmosis (eg, southeastern United States) or coccidioidomycosis (eg, San Joaquin Valley, CA), a detailed history of pet contact (eg, cats or kittens, which can transmit toxoplasmosis and cat-scratch disease), and exposure to ill contacts, particularly individuals known to have tuberculosis, are also important (Box 100.2). In addition, it is important to obtain a history of chemical exposure and steroid use.

Physical Examination

When evaluating a child with lymphadenopathy, the enlarged nodes should be examined and measured at their widest diameter and evaluated for evidence of erythema, tenderness, and warmth, all of which are suggestive of infection. The characteristics of the

Box 100.2. What to Ask

Lymphadenopathy

- How long have the nodes been enlarged?
- Was the child sick before the swelling began?
- Does the child currently have any symptoms, such as fever, weight loss, pallor, night sweats, or anorexia?
- Does the child come in contact with any animals, particularly cats?
- Has the child traveled anywhere?
- Is the child taking any medications?
- Has the child been in contact with anyone who is ill?

Table 100.2. Differential Diagnosis of Lymphadenopathy in Children

Diagnostic Category	*Clinical Features*	*Laboratory Features, Initial Radiologic Studies*
Infections		
Viral (EBV, CMV, rubella, HIV)	Usually generalized, not purulent or tender; may have hepatosplenomegaly	EBV/CMV with atypical lymphocytes on peripheral blood smear, viral titers, and PCRs
Mycobacterial (TB, atypical mycobacteria)	Usually localized; often tender, red, fluctuant	PPD, chest radiograph, QuantiFERON-TB Gold
Bacterial (staphylococcal and streptococcal infections, cat-scratch disease, tularemia, plague, diphtheria)	Usually localized; often tender, red, fluctuant	Titers (cat scratch), Gram stain/culture
Protozoal (toxoplasmosis)	Generalized	Titers
Spirochete (syphilis)	Usually localized in primary, may be generalized in secondary	Titers
Fungal (histoplasmosis, coccidioidomycosis)[a]	May be generalized	Titers
Neoplastic Conditions		
Hodgkin lymphoma[b]	Often associated with "B" symptoms (eg, fever, weight loss, night sweats), pruritus	ESR (can be >100), LDH, elevated eosinophils, anergy, elevated ferritin, chest radiography
Non-Hodgkin lymphoma	See Hodgkin lymphoma	Abdominal ultrasonography
Leukemia	Generalized lymphadenopathy, hepatosplenomegaly, petechiae, purpura, pallor	Cytopenias (ie, leukopenia, neutropenia, thrombocytopenia, anemia); lymphocytosis and blasts on peripheral blood smear (not always absent), hyperuricemia, hyperkalemia, hyperphosphatemia, elevated LDH
Solid tumors (eg, rhabdomyosarcoma, neuroblastoma)	Depends on location and character of underlying malignancy	Imaging such as CT or MRI
Langerhans cell histiocytosis	Eczema, failure to thrive, bony lesions, diabetes insipidus, proptosis, hepatosplenomegaly, and early teeth eruption all possible	Characteristic pathology with Birbeck granules and CD1a+
Sinus histiocytosis with massive lymphadenopathy	Lymphadenopathy involving cervical, axillary, inguinal, and mediastinal nodes	Presence of histocytes in lymph nodes as well as extra nodal sites
Autoimmune Disorders		
Juvenile idiopathic arthritis[c]	Generalized lymphadenopathy seen in systemic form (eg, Still disease), such as fever, hepatosplenomegaly, evanescent rash, arthritis	ESR, anemia, negative ANA, and rheumatoid arthritis in JRA (eg, Still disease)
Lupus[d]	Arthritis, butterfly facial rash, effusions (lung, joint, cardiac), CNS involvement, nephrotic syndrome	ESR; positive ANA; anti-double-stranded DNA; C3, C4, or CH50 levels; anemia; low platelets; proteinuria
Other		
Storage disorders (eg, Niemann disease, Gaucher disease)	Generalized lymphadenopathy, hepatosplenomegaly	Characteristic pathology on biopsy
Drugs (eg, phenytoin)	Generalized lymphadenopathy	None
Sarcoidosis[e]	Bilateral hilar lymphadenopathy, noncaseating granulomas (ie, lung, liver)	Serum angiotensin-1–converting enzyme, serum lysozyme

Abbreviations: ANA, antinuclear antibody; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; JRA, juvenile rheumatoid arthritis; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; PPD, purified protein derivative; TB, tuberculosis.

[a] Suspicion should be raised based on regional incidence.

[b] Common among individuals of higher socioeconomic status, adolescents.

[c] Equal incidence in boys and girls.

[d] Increased incidence in girls.

[e] In black individuals and those of Irish heritage.

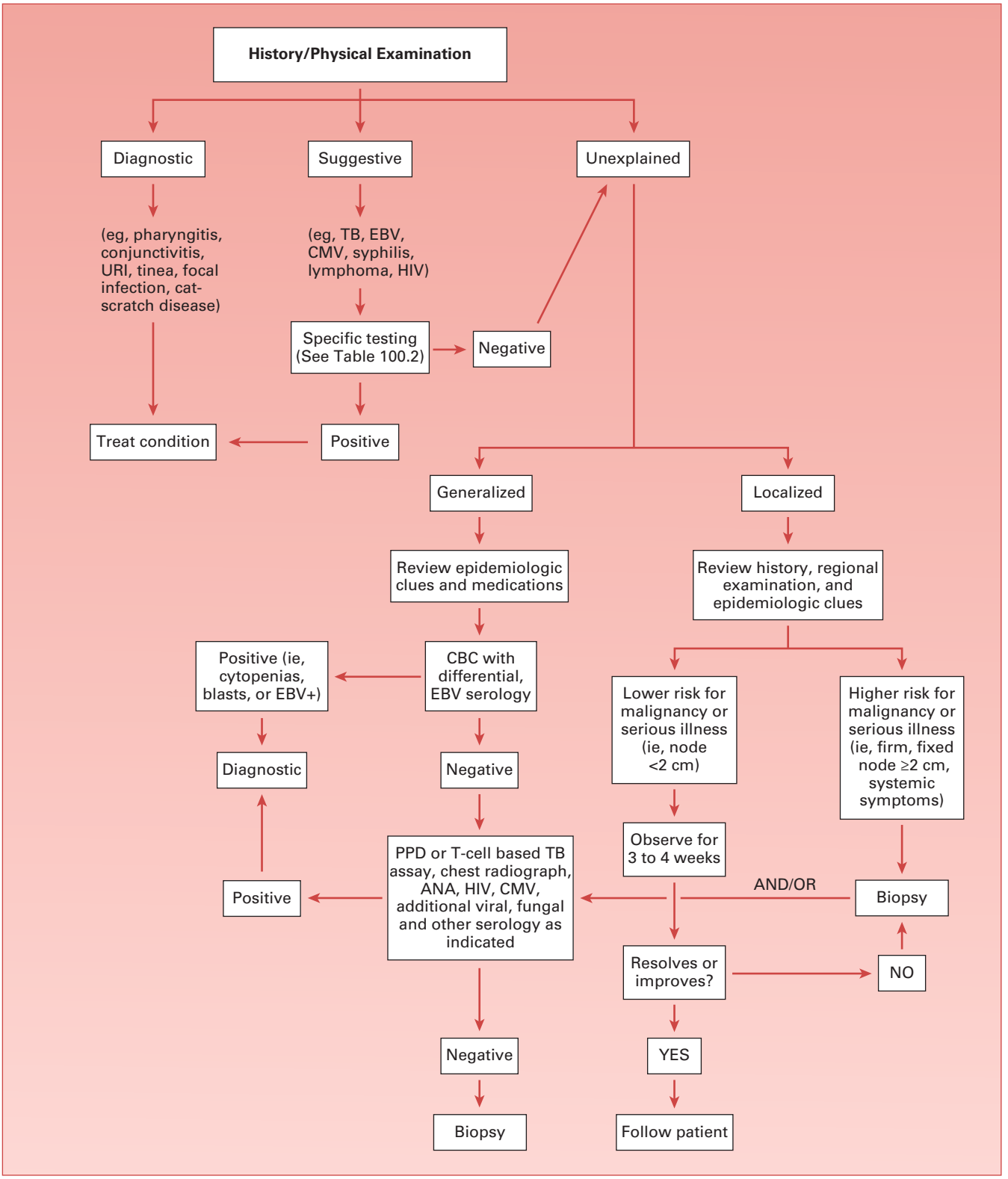

Figure 100.1. Approach to the management of lymphadenopathy.

Abbreviations: ANA, antinuclear antibody; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PPD, purified protein derivative; TB, tuberculosis; URI, upper respiratory infection.

Adapted with permission from Ferrer R. Lymphadenopathy: differential diagnosis and evaluation. *Am Fam Physician*. 1998;58[6]:1313–1320.

enlarged lymph node should be noted (eg, soft, firm, rubbery, mobile, matted, tender, discrete). The surrounding skin and soft tissue region that is drained by the involved lymph node should be examined for signs of inflammation or skin breakdown. The extent of the lymphadenopathy should be determined, and the presence or absence of hepatosplenomegaly should be noted.

Laboratory Tests

In most cases, a thorough history and physical examination can establish the likely diagnosis without any laboratory testing. If studies are deemed necessary, a complete blood cell count, peripheral blood smear, tests of renal and hepatic function, and tumor lysis laboratory tests are useful to screen for an underlying systemic illness that may be associated with lymphadenopathy. Lymphocytosis with atypical lymphocytes on peripheral blood smear is consistent with a viral etiology, such as EBV or CMV. Leukocytosis with a left shift is suggestive of a bacterial etiology. Cytopenias or blasts on peripheral blood smear are concerning for leukemia. Uric acid, phosphorus, and lactate dehydrogenase are typically elevated in the setting of leukemia or lymphoma. An erythrocyte sedimentation rate is nonspecific but may be helpful. Depending on the clinical scenario, serum antibody studies and viral polymerase chain reactions for various infections may be warranted (ie, EBV, CMV, HIV, *Bartonella henselae* for cat-scratch disease, *Bartonella quintana* for trench fever). Additionally, testing for tuberculosis or serologic tests for fungal disease should be considered. Newer T-cell–based assays for tuberculosis, such as interferon-γ release assay or QuantiFERON-TB Gold, have been suggested for testing any individuals age 5 years and older with suspected infection. In younger children, tuberculin skin testing is still suggested. In lupus and juvenile idiopathic arthritis, an antinuclear antibody assay may be positive and complement levels may be reduced.

If infectious lymphadenitis is suspected, an aspirate for a Gram stain and culture may be helpful, particularly if the infection has been unresponsive to empiric antibiotics. If *any* concern exists for malignancy, however, a fine needle aspiration is *not* the preferred method for diagnosis. An excisional biopsy should be performed so that the entire lymph node and its architecture can be visualized and adequate samples for testing are available. See Figure 100.1 for the suggested approach to generalized lymphadenopathy in children.

Imaging Studies

A chest radiograph should be obtained from any child with significant lymphadenopathy if suspicion exists for an underlying systemic process. If leukemia or lymphoma is suspected, a chest radiograph is obtained to evaluate for an anterior mediastinal mass. Other imaging studies are not routinely performed; however, if the nature of an enlarged lymph node requires further definition, ultrasonography can be performed. Massive lymphadenopathy in the head and neck region may warrant evaluation with computed tomography or magnetic resonance imaging. In the setting of malignancy, additional radiographs are obtained for staging purposes.

Management

Management is dictated by the underlying cause of lymphadenopathy (Figure 100.1). Cervical lymphadenopathy associated with URIs typically resolves without intervention. Bacterial lymphadenitis can be managed with a trial of antibiotics with antistaphylococcal and antistreptococcal coverage. With the exception of cervical adenopathy caused by atypical mycobacteria, which requires surgical removal, underlying fungal and mycobacterial diseases should be managed with appropriate antifungal or antibacterial agents. Malignancies may require multimodal therapy with surgery, chemotherapy, or targeted therapy or radiation, depending on the specific diagnosis and stage (see Chapter 152).

Prognosis

The outcome of lymphadenopathy depends entirely on the underlying etiology. In most cases, the cause is infectious and the lymphadenopathy is self-limited or resolves with the use of appropriate antibiotics. Lymphadenopathy associated with an underlying systemic illness may have a more chronic or relapsing course, depending on the disease.

CASE RESOLUTION

The bilateral nature of the swelling and lack of tenderness of the nodes are quite worrisome and are suggestive of systemic involvement. The girl underwent a throat culture and an intermediate purified protein derivative skin test, and a chest radiograph was obtained; the results of all these evaluations were negative. A complete blood cell count revealed leukocytosis with 28,000 white blood cells per deciliter (60% lymphocytes) with a normal hemoglobin and platelet count. A heterophile test result for infectious mononucleosis was positive. Supportive measures were implemented, and the child made a complete recovery in 3 weeks.

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PART 8

Cardiovascular System

CHAPTER 101

Heart Murmurs

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CASE STUDY

A 6-year-old girl is brought to the office for a physical examination for school. Her medical history is unremarkable, and her growth and development have been normal. She is asymptomatic. Her physical examination is normal except for a grade 2 of 6 low-pitched vibratory systolic ejection murmur that is loudest at the left lower sternal border, with radiation to the apex and upper sternal border. The murmur increases to grade 3 of 6 with the patient in the supine position.

Questions

1. What is the significance of a heart murmur in an asymptomatic child? How reassuring are a negative history and the absence of other physical findings?
2. What workup should be done by the primary care physician?
3. What are the consequences of not recognizing a murmur as being innocent? What are the consequences of an inadequate workup?
4. When should the physician refer a child to a specialist for consultation?

Asymptomatic children with heart murmurs are commonly encountered by physicians. A murmur is a finding rather than a medical sign or symptom, because it is detected incidentally at an examination conducted for another purpose.

Correct assessment of the significance of a heart murmur is important to ensure appropriate treatment of children with heart disease. Complications of undiagnosed cardiac disease in children include progressive hemodynamic impairment, endocarditis, and even sudden death.

The misinterpretation of an innocent murmur as organic in nature can also be a source of stress, primarily in the form of parental anxiety. Unnecessary restriction of activities may result, which can have a negative effect on children's school and social lives as well as self-image. As adults they may be denied health insurance, life insurance, and certain types of employment. Additionally, misdiagnosis is financially costly and uses limited resources, with unnecessary tests and doctor visits, as this "nondisease" is evaluated and followed.

Epidemiology

An estimated 50% of healthy children have heart murmurs. The overall incidence of congenital heart disease (CHD), including symptomatic cases, is just under 1%, most of which are identified prenatally (by ultrasonography) or in the newborn period (by pulse oximetry screening [see Chapter 103]). Some children with CHD have no murmur. Therefore, approximately 98 of 100 murmurs noted during childhood are "innocent" (ie, have no organic basis).

Clinical Presentation

Heart murmurs are usually detected on routine examination for well-child care or on evaluation for an unrelated problem. Innocent murmurs are not associated with signs or symptoms, because they are normal findings. Most of the symptoms sometimes associated with organic murmurs (ie, murmurs of heart disease) are related to the presence of congestive heart failure (CHF) (see Chapter 104) and usually become evident during infancy. Some children with murmurs come to medical attention with reports of exercise intolerance or chest pain. It is necessary to determine whether these problems are truly referable to the heart, which is uncommon (see Chapter 105).

The noting of a murmur in a child for the first time may be considered a "new murmur," which in the adult can be a serious finding heralding new onset of acquired heart disease, such as mitral insufficiency resulting from poor ventricular function or aortic insufficiency resulting from infective endocarditis. In the pediatric patient, these findings are rare. Much more commonly, a murmur not previously noted may be heard for the first time for benign reasons. These murmurs are referred to as innocent murmurs and may vary by patient age or the position in which the child is examined. Previously very soft murmurs may be more pronounced under different conditions, such as fever or anxiety. Murmurs that are predominantly audible in the supine position may not have been noted when the child was examined only in the upright position, or vice versa. The lower heart rate and better level of cooperation of the child, compared with the infant, may allow the examiner to identify a murmur not heard on previous examinations.

Pathophysiology

A murmur is a sustained sound that can be detected with a stethoscope placed on the chest. This sound is produced by turbulence of blood flow in the heart or great vessels. This turbulence may be caused by structural abnormalities (eg, aortic valve stenosis), benign or normal flow patterns (discussed later in this chapter), or exaggeration of normal flow patterns (as in high-output states, such as fever, exercise, anxiety, or anemia, and sometimes termed "functional").

Not all significant heart disease in children is heralded by a murmur. Structural heart disease may be silent and be indicated by other findings. For example, transposition of the great arteries results in cyanosis, anomalous pulmonary venous return in pulmonary edema and hypoxia, and anomalous origin of the left coronary artery from the pulmonary artery in CHF. Acquired heart disease, such as Kawasaki disease, myocarditis, or cardiomyopathy, often produces no murmur.

The common innocent murmurs are better recognized than understood. Because they occur in normal, healthy individuals, few hemodynamic or anatomical data exist to correlate with the murmur, and in some cases pathophysiology is conjectural. Still murmur, which once was thought to be the result of easily appreciated aortic valve flow, is now believed to result from vibration of normal fibrous bands ("false tendons") that cross the left ventricle. This murmur may also be heard in children who have undergone spontaneous closure of a membranous ventricular septal defect, with a small residual aneurysm in the septum. The pulmonary flow murmur seems to be caused by normal flow across the pulmonary valve, perhaps made more apparent because of high cardiac output, close proximity to the chest wall, and, in adolescent females, mild anemia. The venous hum is attributed to turbulence at the confluence of the innominate veins, which is exacerbated in the upright position by gravity.

The *physiologic peripheral pulmonic stenosis murmur*, which is an innocent murmur found in newborns, is produced by turbulence at the origins of the left and right pulmonary arteries. Because less than 10% of the combined ventricular output of the fetus goes to these branches, they are small and arise at a sharp angle from the main pulmonary artery. When postnatal circulation abruptly requires the entire cardiac output to enter these vessels, a relative stenosis is encountered. This physiologic stenosis resolves gradually with remodeling of the pulmonary artery tree by 2 to 3 months of age.

Differential Diagnosis

In healthy children, the differential diagnosis of a heart murmur includes innocent murmurs and murmurs resulting from structural lesions, most of which are congenital. Although the specific features of a particular murmur usually provide many clues to the diagnosis, in the current era, the main task of the primary care physician is to correctly identify the patient who requires cardiology referral. It is therefore important to develop and maintain auscultatory skills. No written or visual material is a good substitute for practice with recordings and actual patients. A good quality stethoscope, with both diaphragm and bell correctly sized for the patient, and snugly fitting but comfortable earpieces, is essential. Conditions should be optimized: The patient should be kept comfortable and, if necessary, distracted, and extraneous environmental noise should be minimized.

Some features may alert examiners to the organic nature of a murmur. Although very loud murmurs (grades 4–6; ie, with associated precordial thrill) usually are not innocent, some innocent murmurs may be as loud as grade 3, particularly with high cardiac output (eg, fever, anxiety, anemia). Diastolic murmurs and continuous murmurs, other than the easily recognizable venous hum, are usually pathologic, as are high-pitched and harsh murmurs, which are better heard with the diaphragm of the stethoscope. Murmurs that change strikingly with body position are rarely the result of CHD.

The common innocent murmurs of childhood are recognizable on auscultatory examination. *Still murmur*, or the "innocent vibratory murmur," is a low-pitched, vibratory, or musical murmur that sounds like a groan. Because of its low frequency, the murmur is better heard with the bell. It is loudest at the left lower sternal border but often is distributed widely over the precordium. This murmur often is quite loud, particularly in the supine position, and is extremely common in school-age children, although it also may be heard in the infant. The characteristics of the murmur itself are diagnostic, although the absence of other findings is supportive.

The *pulmonary flow murmur*, which usually is heard in older children, is a short, blowing systolic ejection (ie, crescendo-decrescendo) murmur localized to the left upper sternal border. It may be louder with the patient in the supine position.

The *venous hum* is a soft continuous murmur, similar to the sound heard in a seashell. Because of its constancy, it is often overlooked. This murmur is commonly heard in preschool and school-age children. Loudest in the right infraclavicular area, it may also be heard on the left. This murmur is highly variable with head and neck position and compression of the neck veins, which may increase or diminish it. It usually disappears with the patient in the supine position.

The physiologic peripheral pulmonic stenosis murmur, an innocent murmur found in newborns, is best heard at the upper left sternal border. This blowing systolic ejection murmur radiates strikingly over the lung fields into the back and both axillae. Typically, it disappears by 3 months of age, whereas the murmur of true stenosis of the pulmonary arteries persists.

Evaluation

History

The history may be helpful in assessment of the child with a murmur. If a thorough history shows that the child has no symptoms, this suggests the absence of severe heart disease and helps exclude many major or complex defects as well as CHF. The absence of symptoms does not, however, exclude several common defects that may require intervention (Table 101.1).

The most common cardiac symptom reported by children or their parents is easy fatigability (Box 101.1). This is difficult to quantitate. Determining exercise intolerance on the basis of history is quite subjective; of course, it may be the result of noncardiac

Table 101.1. Common Organic Heart Murmurs in Asymptomatic Children

Lesion	*Other Clues*
Atrial septal defect	Fixed split second heart sound S_2
Ventricular septal defect (small to moderate)	Loud heart sounds
Patent ductus arteriosus (small to moderate)	Full or bounding pulses
Pulmonic stenosis	Systolic ejection click
Aortic stenosis	Systolic ejection click; suprasternal thrill
Coarctation of the aorta	Weak or absent femoral pulses

Box 101.1. What to Ask

Heart Murmur

- Is the child easily tired? Is the sleeping/napping pattern normal for age?
- Does the child keep up with other similarly aged children?
- If the child is having a good time—for example, at a park or a party—how is the child's endurance?
- Does the child have a family history of congenital heart disease?
- Was the child exposed antenatally to possible cardiac teratogens, such as maternal diabetes?
- Does the child ever report chest pain, either at rest or with activity?
- Does the child ever appear blue?
- Does the child perspire excessively?

causes and may be unrelated to the murmur. Easy fatigability during infancy may be reported as slow or poor feeding. Chest pain, a common symptom in adults with heart disease, is rarely cardiac in origin in children (see Chapter 105). A history of rapid breathing, excessive sweating, and other symptoms referable to CHF is suggestive of organic heart disease. Central cyanosis (ie, involving the oral mucosa rather than the perioral area or the fingers) may be reported occasionally by parents of children with cyanotic CHD but often is not recognized.

Physical Examination

The physical examination often gives strong clues to the cardiac diagnosis beyond the murmur itself. Even in children with known CHD, the nonauscultatory portions of the examination are critical in assessing the cardiac status (ie, how the patient is tolerating the defect). Vital signs, preferably obtained with the child at rest or sleeping, yield information about cardiac status more than specific diagnosis. Tachypnea and tachycardia are present in CHF. A normal resting respiratory rate (ie, <60 breaths/minute in infants) argues strongly against CHF. Blood pressure is normal in most patients with CHD. It may be useful to measure blood pressure in the legs, especially if coarctation of the aorta is suspected because of diminished pulses in the lower extremities or a pulse oximetry difference between upper and lower extremities.

The growth pattern may reflect the presence of any chronic illness, including hemodynamically significant CHD. Affected patients, particularly infants and children with large left-to-right shunts (with or without CHF) gain weight poorly. Height and head circumference are usually normal, although in more severe or prolonged situations height may also be affected.

A complete cardiac examination should be performed. The patient should be assessed for chest asymmetry, which is a sign of long-standing cardiomegaly. Whether the precordial impulse is hyperdynamic should be noted. Extra sounds (eg, clicks, rubs, gallops) should be noted as well. The physician should determine whether the second heart sound is normal in intensity and in width and motion of splitting (ie, variation with respiration).

Additional pertinent findings include lethargy, dysmorphic features suggestive of a genetic syndrome, noncardiac anomalies commonly associated with CHD, central cyanosis, and clubbing. Hepatomegaly occurs in children with CHF. The peripheral pulses should be normal in volume, neither diminished (eg, pedal pulses in coarctation) nor bounding (eg, in patent ductus arteriosus), and equal in all extremities. The temperature and capillary refill of the extremities in children who are not chilled reflect adequacy of the peripheral circulation.

Diagnostic Studies

Routine laboratory studies are not warranted in the evaluation of most murmurs. Electrocardiography is indicated in cases in which heart disease is known or strongly suspected, but a normal echocardiogram may not rule out significant CHD, particularly in the infant. A chest radiograph may be helpful in this setting, but its potential benefits usually are outweighed by the risks of discomfort and radiation exposure. In the case of some tests, such as echocardiography and magnetic resonance imaging, the manner in which the examination is performed varies depending on the suspected diagnosis; direct input from a cardiologist may be necessary to maximize the yield from these studies. Such tests are not suitable for screening purposes and should be obtained only after consultation with a pediatric cardiologist.

Management

If a heart murmur is suspected of being organic in origin because of its features or associated findings, referral to a pediatric cardiologist is indicated. For the young infant (particularly the newborn), the level of concern is high because of the serious risks inherent in ductus-dependent defects (see Chapter 103), which may present with a simple murmur. Newborns with critical heart pathology typically are identified before hospital discharge, particularly in areas in which pulse oximetry screening is routinely performed. Thus, a newborn with a murmur who "passes" the oximetry screen and has an otherwise normal examination (including femoral pulses) does not require echocardiography or cardiology consultation on an emergent basis.

Although urgency is not warranted in the case of a child who is asymptomatic, parental and physician anxiety can best be allayed

by proceeding to consultation promptly (ie, within weeks). In some cases, a repeat examination may be useful before deciding whether to consult a specialist, particularly if the murmur is initially heard under nonphysiologic conditions, such as fever. Typically, the determination of whether to perform tests and which to perform is best left to the specialist. Not all cardiologists perform all tests on all patients. Because pediatric cardiologists are particularly skilled and experienced in cardiac auscultation, an examination by a confident specialist, at a cost which is an order of magnitude less than that of echocardiography, may be all that is indicated. Innovative methods are under development to enable long-distance auscultation via telemedicine using digital recordings obtained by the primary physician, and even computer-aided auscultation of heart murmur. These approaches may be particularly helpful in overcoming geographic challenges in underserved populations or populations distributed over a large geographic area (ie, rural populations).

Management of organic heart disease in infants and children is also best done by specialists. Treatment may include medications, interventional catheterization, or cardiac surgery. Communication between the primary care physician and the cardiologist, however, is essential to delivery of optimal patient care.

If the murmur is innocent, physicians must complete the steps listed in Box 101.2.

Box 101.2. Steps for Managing an Innocent Heart Murmur in the Pediatric Patient

1. Inform the child and family about the presence of the murmur. Even if the murmur is benign, patients have a right to know that it was heard. In addition, they are likely to be examined by other clinicians who will report it, which may result in the erroneous suspicion of either a new murmur or negligence on the part of the first examiner.
2. Clearly explain the diagnosis to the parent(s)/guardian(s) and, depending on patient age, the child. It is essential that they understand that this is a normal finding rather than a minor abnormality. In some cases, it may be appropriate to notify teachers or athletic coaches to prevent misunderstanding. Physicians must stress that no further evaluation is necessary and no restrictions are indicated. Printed brochures that explain innocent murmurs are available from organizations such as the American Heart Association.
3. Document the description of the murmur and the diagnosis itself in the medical record. If the examiner possesses a digital stethoscope, a recording of the murmur may be entered into the patient's electronic health record. A murmur that is clearly and unequivocally innocent, with no evidence of heart disease, should not affect the child's access to insurance, participation in sports, etc. Medical documentation also helps protect patients from unnecessary reevaluations in the future.
4. Proceed no further. No laboratory studies or consultations need be performed. If the evaluation has been completed by a specialist because of suspicion of CHD by the referring physician, no follow-up with the specialist is indicated. The child is referred back to the primary care physician.

Prognosis

The prognosis for children with heart murmur depends on the cause of the murmur. Children with an innocent murmur, who by definition have normal hearts, have a normal prognosis—with 1 exception. If parents or guardians mistakenly believe their children to have heart disease, they may treat the children inappropriately (eg, unnecessary testing, restriction of activities). As a result, children may develop sedentary habits and inferior self-image.

With appropriate medical attention, the prognosis is normal or near normal in most patients with CHD. Children with minor defects not requiring intervention (eg, small ventricular septal defect, mild pulmonic stenosis) need only infrequent cardiology follow-up visits. Endocarditis prophylaxis, previously recommended in such cases, is no longer recommended because of its high risk/benefit ratio. With the development of refined cardiac surgery and interventional catheterization, even children with the most complex cardiac anomalies currently have a good outlook with respect to both quality of life and life expectancy.

CASE RESOLUTION

The healthy girl with no history of cardiovascular symptoms has a heart murmur and an otherwise unremarkable physical examination. The murmur is a typical Still (ie, innocent vibratory) murmur, which is identifiable by its low-pitched, vibratory quality. No further evaluation is necessary. The diagnosis is explained, the girl and her parents are reassured, and the murmur and diagnosis are noted in the medical record.

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CHAPTER 102

Palpitations

Robin Winkler Doroshow, MD, MMS, MEd, FAAP, and Nefthi Sandeep, MD

CASE STUDY

A previously healthy 10-year-old girl presents to your office with a report of an episode of a "racing heart." The episode occurred approximately 1 week before the clinic visit while she was watching television. Her heart suddenly started pounding hard, and the sensation stopped just as suddenly approximately 30 minutes later. During the episode, the child's mother felt the girl's chest and noted that her heart was beating extremely fast and hard. The child looked scared during the episode but was in no respiratory distress and was alert. Her parents drove her to the local emergency department, but the symptoms stopped en route. On arrival in the emergency department, the girl was fine and had normal vital signs and physical examination and a normal result on electrocardiography. In retrospect, she recalls having had brief such episodes in the past.

Questions

1. What is the significance of palpitations in an otherwise well child?
2. How likely is this symptom to be cardiac in origin, and if so, how likely is it to be life-threatening?
3. How can transient cardiac events be documented?
4. What does the primary care physician need to do and know before referring the child to a cardiologist?

The term *palpitations*, which is currently used more by medical personnel than by patients, refers to a sensation of increased awareness of the heart beating faster, harder, or less evenly than expected. Frequently used lay terms for this perception are "racing," "fluttering," or "pounding of the heart." Some patients simply report a sudden unexplainable feeling of being afraid, or they may interpret the symptom as pain or other indescribable discomfort in the chest.

Epidemiology

The prevalence of palpitations is unknown. Palpitations are a fairly common reason for referral of pediatric patients to cardiologists, although it is a significantly less common reason than murmurs or chest pain. Because articulating this complaint requires significant verbal skills as well as bodily awareness, it is not usually reported before age 3 or 4 years; beyond this threshold, it may occur at any age. Cardiac arrhythmia, which is the most likely significant cause of this symptom, occurs at any age—even in utero—but the presenting symptom in younger patients usually reflects secondary or tertiary physiological changes, such as altered mental status, color change, syncope, or respiratory distress.

Clinical Presentation

As with chest pain, patients' descriptions of symptoms of palpitations are quite varied. Palpitations are almost always episodic, with a sudden sensation of the heartbeat taking the child by surprise. Because this feeling may be alarming or at least disconcerting (even to adults), the patient may not have been a reliable observer and thus, the report of the episode or episodes may be lacking in clarity or detail. The sense of alarm may stem from the unexpected nature of onset of the palpitations, interpretation in an older child or an adult observer that a dangerous cardiac event (eg, heart attack) is occurring, or misinterpretation of a rapid heartbeat as a reflection of fear. It is also not unusual to see a child entirely unconcerned about this symptom accompanied to the visit by an extremely concerned parent.

Almost all patients with palpitations report its occurrence in the absence of other medical issues, as in the case study at the beginning of this chapter.

Pathophysiology

Palpitations are a subjective symptom and may reflect a cardiac issue (most commonly arrhythmia), anxiety, or simply increased somatic awareness. Only the first of these issues has a significant component of abnormal physiology.

The degree to which cardiac function may be compromised in cases of arrhythmia depends on the nature of the rhythm, heart rate, duration of the episode, and presence or absence of underlying cardiac disorders, whether congenital or acquired. In ventricular tachycardia (VT), the heart rate is usually in the range of 150 to 180 beats per minute, and filling is not seriously impaired; however, loss of atrioventricular synchrony and inefficient ventricular emptying result in poor cardiac output in most cases. In addition, VT can deteriorate to ventricular fibrillation, with essentially no functional cardiac output, which is a life-threatening situation. Supraventricular tachycardia (SVT) is by far the most frequently diagnosed sustained arrhythmia in the pediatric population. It is characterized by a substantially higher heart rate (often >250 beats per minute), with relatively less time in diastole and more in systole.

This increased heart rate results in compromise of ventricular filling and secondarily of the cardiac output, as well as an unfavorable myocardial supply-demand ratio, which may cause angina-like chest pain. Atrioventricular block is uncommon in otherwise healthy children and is more likely to produce presyncope or syncope than palpitations; however, the latter may also occur. Atrial ventricular block impairs cardiac output by a decrease in ventricular rate and loss of atrioventricular synchrony.

Some patients report erratic, very brief pounding sensations caused by single premature ventricular contractions (PVCs), whereas other patients are unaware of this common arrhythmia (Figure 102.1). Those patients who do perceive them are sensing the increased cardiac output of the immediate post-PVC beat as a "thump" and rarely experience associated symptoms. Premature atrial contractions are quite common but are rarely perceived by the patient.

Palpitations related to anxiety disorders often are associated with other catecholamine-induced symptoms, such as dyspnea or tremor; these somatic symptoms may dominate over psychiatric symptoms and divert the physician's attention from the pursuit of a psychological cause.

Differential Diagnosis

The differential diagnosis of palpitations is summarized in Box 102.1. In cases of sudden onset of isolated rapid pounding of the heart, SVT (which includes reentrant SVT, junctional tachycardia, ectopic atrial tachycardia, and atrial flutter) is the most common cardiac cause of such pounding (Figure 102.2). One study found that 35 of 238 consecutive children whose rhythms were transmitted transtelephonically during palpitations had SVT; no other significant arrhythmias were found in the other 203 patients. Despite the rarity of them, other tachyarrhythmias and bradyarrhythmias must be considered, however, because of the poorer prognosis associated with them and the importance of instituting therapy to manage them.

Sinus tachycardia in the absence of anxiety may be experienced by individuals with decreased stroke volume, such as patients with myocarditis or cardiomyopathy, either of which may manifest with palpitations. Children undergoing stimulant therapy for attention-deficit/hyperactivity disorder experience palpitations with surprising infrequency, perhaps because their slight overall increase in heart rate is chronic rather than episodic. Cardiac arrhythmias in this setting are no more common than in the general pediatric population. However, stimulants in the form of so-called energy drinks are becoming increasingly popular in the adolescent and preadolescent population and may result in inappropriate sinus tachycardia. Caffeine is the main active ingredient in most energy drinks. Other beverages, including guarana, also have inotropic and chronotropic properties. Use of drugs, such as amphetamines, likewise may result in sinus tachycardia, but patients rarely experience symptomatic discomfort. Hyperthyroidism is associated with sustained sinus tachycardia, which patients occasionally report and can also progress to significant cardiac arrhythmias.

Psychogenic palpitations are quite common in childhood, occurring in approximately 50% of pediatric patients with anxiety disorders and panic disorder. Such palpitations may be the presenting symptom and should not be dismissed by the physician as

Box 102.1. Differential Diagnosis of Palpitations in Children and Adolescents

Cardiac Arrhythmias

- Atrioventricular block (rare cause)
- Premature atrial contractions (uncommon cause)
- Premature ventricular contractions (common cause)
- Sinus tachycardia
  - Caused by high-output states, such as hyperthyroidism and anemia (uncommon cause)
  - Caused by low cardiac output, such as in patients with myocarditis or cardiomyopathy (rare cause)
  - Caused by stimulants, such as amphetamines, β agonists, and caffeine (common cause)
- Supraventricular tachycardia (common cause)
- Ventricular tachycardia (rare cause)

Psychogenic

- Hypochondria (common cause)
- Panic attacks and other anxiety disorders (uncommon cause)
- School phobia (common cause)

Other

- Somatic hyperawareness (common cause)

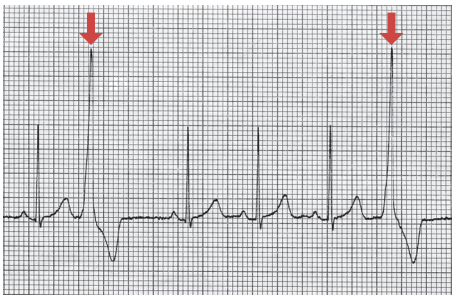

Figure 102.1. Electrocardiogram showing premature ventricular contractions (arrows).

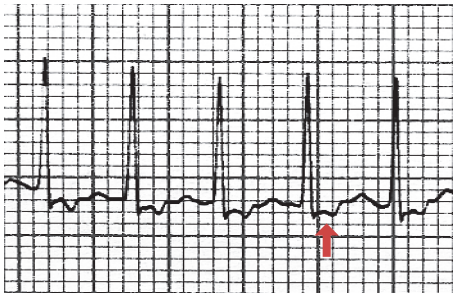

Figure 102.2. Electrocardiogram showing supraventricular tachycardia at 257 beats per minute. Note ST depression (arrow) caused by relative myocardial ischemia.

unimportant. For patients in whom anxiety disorders are ruled out, diagnosing somatic hyperawareness, such as is often seen in healthy adolescents (eg, "My heart speeds up when I take a test"), may reassure the patient that there is no underlying cardiac disease.

Evaluation

The history and documentation of cardiac rhythm are critical to the evaluation of children with palpitations. The history guides the physician in determining which direction to pursue and, in particular, how extensive an arrhythmia workup is required. When arrhythmia is suspected, documentation (ie, "capturing" the arrhythmia) is essential prior to intervention.

Obtaining a complete history and physical examination helps the pediatrician establish a level of concern about the likelihood of cardiac causes for the palpitations. That, in turn, guides elective referral to a cardiologist, emergent referral to an emergency department (ED) or hospital, elective referral to a psychologist or psychiatrist, or, alternatively, management of the condition without further referral.

History

It is important to obtain as much descriptive information as possible directly from the child as well as any witnesses (Box 102.2). Language such as "very fast" may be interpreted differently by different people and, thus, is not helpful. A witness can also report whether the patient had a change in color, respiratory pattern, or mental status.

Palpitations of abrupt onset and offset are more likely to reflect paroxysmal cardiac arrhythmias, while sinus tachycardia resulting from stimulants or anxiety is more likely to have a gradual onset and resolution. Some arrhythmias may be triggered by certain events or actions, such as exertion, emergence from anesthesia, or exposure to stimulants (eg, β agonists).

Box 102.2. What to Ask

Heart Palpitations

- What does it feel like? If the heartbeat is fast, how fast?
- What symptoms are associated with the palpitations?
- Do the symptoms start gradually or abruptly? How do they end? Can the patient cause them to end?
- How frequent are the episodes, and how long do they last?
- Are the episodes precipitated by certain events?
- How disruptive are these symptoms to activities of daily living?
- Does the child have a history of cardiac problems, such as congenital heart disease or other symptoms, that point to an underlying defect?
- Did the onset of these episodes correlate with other life or medical events?
- Is the child taking or using stimulant medication or beverages that might be contributing to these symptoms?
- Is there a family history suggestive of cardiac arrhythmia, such as sudden unexpected death or long QT syndrome?

The presence or absence of associated symptoms may help determine the seriousness of a cardiac event. Ventricular arrhythmias, such as sustained VT, often cause an abrupt decrease in cardiac output, resulting in loss of consciousness or even sudden death. Brief episodes of SVT may not be associated with any symptoms other than the palpitations themselves; however, a sustained episode of SVT may be associated with fatigue, breathlessness, chest pain, nausea, or dizziness.

Most children reporting palpitations have no relevant medical history. However, patients with past history of congenital heart disease (particularly if it was treated surgically), inflammatory heart disease (eg, myocarditis), or exposure to cardiotoxins (eg, anthracycline chemotherapeutic agents) are more likely to have experienced a significant arrhythmia than others and are less likely to tolerate arrhythmia well. In these settings, prompt and thorough evaluation is essential. As mentioned previously, if patients become alarmed, they also may experience symptoms reflective of increased catecholamine output (eg, breathlessness, pallor), thereby complicating the assessment. These additional symptoms may respond to reassurance that there is no underlying cardiac disease even when the palpitations persist.

The physician must also elicit family history for evidence of heritable rhythm disorders (eg, long QT syndrome [LQTS]) or events (eg, unexpected sudden death) that may be suggestive of such an inherited disorder.

Physical Examination

The physical examination of the patient presenting with isolated episodic palpitations is rarely contributory. The cardiac rhythm and rate should be noted, but rarely are they directly indicative of a diagnosis. Findings such as a heart murmur or gallop may point toward a previously unidentified underlying cardiac disorder.

Laboratory Studies

In the primary care setting, laboratory studies are rarely necessary to make the determination of whether to refer the patient. Typically, the history and physical examination suffice. In the setting of significant suspicion of arrhythmia, the cardiology consultant considers various studies with a focus on documenting the rhythm during symptoms and seeking evidence of underlying causes of arrhythmia (Table 102.1).

Electrocardiography

Electrocardiography (ECG) is a readily available test that is often diagnostic if obtained during an episode of palpitations. Parents should be instructed to take the child to an urgent care center or ED promptly if the child experiences a prolonged episode (eg, lasting 1 hour) and request that ECG be done immediately on arrival. In the absence of symptoms at the time of the visit, often the ECG does not aid in diagnosis. It is important, however, to evaluate for conditions that predispose a patient to arrhythmia. For example, patients with Wolff-Parkinson-White syndrome are predisposed to SVT, and patients with LQTS are predisposed to VT, in particular, to

Table 102.1. Laboratory Tests Used in the Evaluation of Palpitations in Pediatric Patients

Test	*Information Provided*
ECG	Diagnostic if obtained during symptoms Underlying predisposition to palpitations, such as Wolff-Parkinson-White syndrome or long QT syndrome
Holter monitor (ambulatory ECG)	Passively captures rhythm during symptomatic episodes during a 24- or 48-hour recording period Results are subsequently downloaded
Event detector	Patient-activated Captures rhythm during symptoms over an extended period (eg, 30 days) Real-time download
Implantable monitor	Captures rhythm during symptoms over an extended period (≤3 years) Some devices allow real-time monitoring
Patch monitor	Passively captures rhythm up to 14 days Results are downloaded after the patch has been removed from the patient
Exercise test	Provocation of symptoms or arrhythmia in patients with symptoms that are induced by exercise
Electrophysiology study	Provokes arrhythmias Identifies additional conducting pathways that support arrhythmias Opportunity to intervene (eg, ablation)
Echocardiography	Identifies underlying structural or functional cardiac disorder
Cardiac magnetic resonance imaging	Assesses cardiac anatomy in complex congenital heart disease Evaluates for arrhythmogenic right ventricular cardiomyopathy and scarring caused by myocarditis
Hematocrit	Identifies underlying anemia
Thyroid function tests	Identify underlying hyperthyroidism
Toxicology screening	Identifies drug exposure

Abbreviation: ECG, electrocardiogram.

torsades de pointes (Figures 102.3 and 102.4). Either of these conditions may be only intermittently apparent on a surface ECG; thus, their absence on a single tracing does not exclude them.

Documenting Cardiac Rhythm During Symptomatic Episodes

Documentation of cardiac rhythms during symptomatic episodes is the key to making a diagnosis of arrhythmia and, more often, to ruling out arrhythmia as a cause of palpitations. Multiple techniques are available, each with advantages and disadvantages. The

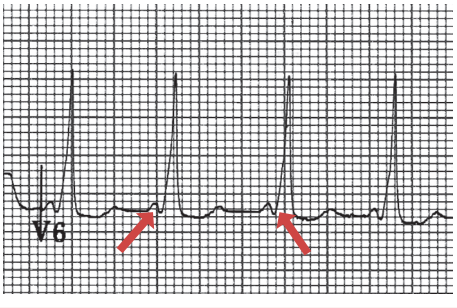

Figure 102.3. Electrocardiogram from a patient with Wolff-Parkinson-White syndrome. Note the short PR interval (left arrow) and the delta wave (right arrow) created by preexcitation.

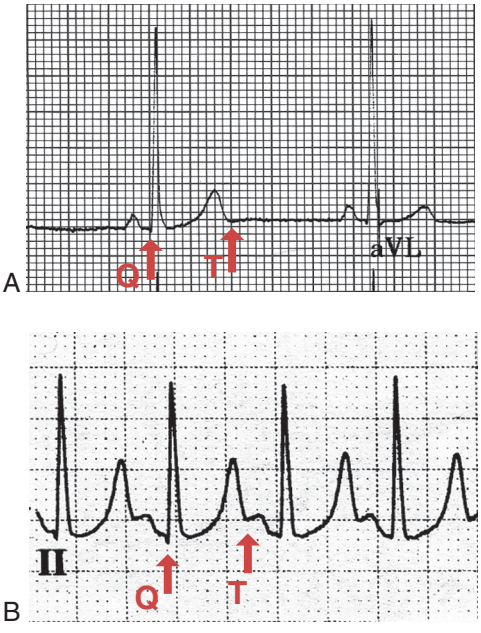

Figure 102.4. A, Normal QT interval. B, Prolonged QT interval. Onset of Q wave and end of T wave indicated by arrows.

Holter monitor is a well-established, sensitive, high-quality random 24- to 48-hour tracing. Only in cases with very frequent (ie, almost daily) palpitations is it likely to capture the symptomatic rhythm itself; however, in some cases subclinical arrhythmias such as brief bouts of SVT may go unnoticed by the patient but are captured on the Holter monitor. The test is readily available but not well tolerated by very young children; it is not monitored by clinicians or technologists in real time; and its value is substantially undermined in cases in which an accompanying symptom diary is not maintained. Similar to ECGs, Holter monitors have excellent specificity (ie, low rate of false-positive results) but poor sensitivity (ie, high rate of false-negative results) resulting from recording during a symptom-free period; thus, a negative result with a Holter monitor does not definitively rule out an arrhythmia. Additional advantages of the Holter monitor include the ability to detect intermittent preexcitation, and the option to quantify the burden of ventricular ectopy.

Less frequent episodic palpitations are more often captured on *event detectors*, also known as *transtelephonic monitors*, which are small devices that can be taken home with the patient for several weeks and used to capture the ECG in the event of symptoms. The recording is transmitted by analog or cellular telephone to a doctor's office or monitoring service. Most transtelephonic monitors are *post-event monitors*, which require the patient to actively produce the recording. With this method, however, the onset of the arrhythmia is not captured. These obstacles may be overcome with use of a *loop-type event recorder*, which continuously records and erases a short loop of ECG. The patient depresses a button when experiencing the symptoms, and the device saves the previous 2 to 3 minutes, thereby enabling capture of the onset of the arrhythmia or even an arrhythmia that has ceased by the time the patient activates the device. Some of these devices may also be programmed to automatically record in certain situations, such as when the heart rate exceeds a selected threshold. Loop recorders require the continuous wearing of stick-on leads with wires, and patient tolerance for them is low.

As technology continues to improve, the range of diagnostic monitor options increases. New *adhesive patch monitoring devices* (eg, Zio, iPatch) are less invasive and less costly than implantable monitors and may be kept in place on the skin for up to 14 days. These devices are wireless, lightweight, single-use, and water resistant. Patch monitors have been studied extensively in the adult population, and early cross-sectional studies in children are promising. The duration of use is an important advantage over the Holter monitor, because 40% to 50% of arrhythmias in ambulatory children occur more than 48 hours from the start of monitoring, which is beyond the reach of a Holter monitor, which records for not more than 48 hours (Figure 102.5). Regardless whether arrhythmia is triggered by a particular symptom, 90% of arrhythmias are diagnosed within 7 days. Current models that have been approved by the US Food and Drug Administration do not allow real-time monitoring; the data can be analyzed only after the patch has been removed from the patient.

Some patients benefit from a small *implantable monitor* (eg, Reveal), which can either automatically record the ECG when certain parameters are met or be activated by the patient. This device is not commonly used in pediatric patients; however, it may be quite helpful for rhythm documentation of infrequent but potentially serious events, such as extended unexplained syncope or near-miss sudden death. Minor surgery is necessary for implantation and for removal up to 3 years later. A newer version, the Reveal LINQ, is injected subcutaneously under local anesthesia. Some models allow real-time monitoring, and others require downloading after removal.

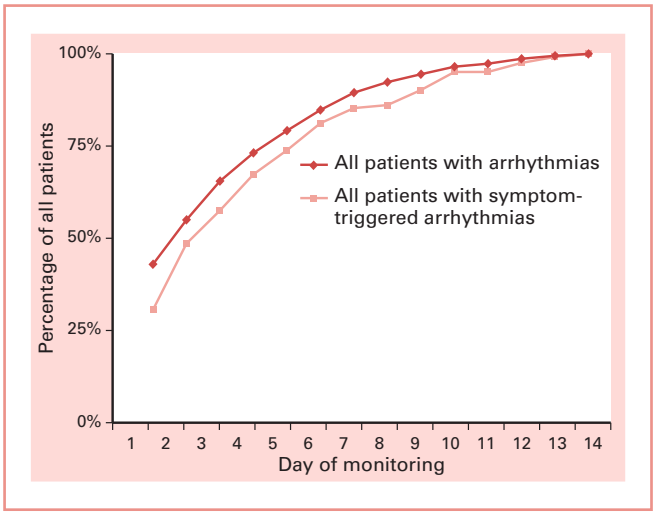

Figure 102.5. Graph showing cumulative yield of arrhythmia detection by patch monitor in children in a 14-day period. Among patients with arrhythmia, the condition was identified by day 7 of monitoring in 90% of patients, but it was identified in only 56% of patients through day 2 of monitoring.
Adapted with permission from Bolourchi M, Batra AS. Diagnostic yield of patch ambulatory electrocardiogram monitoring in children (from a national registry). *Am J Cardiol*. 2015; 115(5):630–634.

Smartphone-based monitoring, which is designed for use in the home, requires purchase of specific hardware and software, followed by deployment by the patient or a caregiver. This method was recently introduced for use in adult cardiology patients, in whom it is well suited to distinguish paroxysmal atrial fibrillation from sinus rhythm. The utility and reliability of this technology in pediatric patients have not yet been demonstrated.

Stress Testing

In select cases in which physical exercise consistently triggers palpitations, a treadmill or bicycle exercise test may occasionally be used to provoke the symptom.

Electrophysiology Study

In the case of strong suspicion for a serious arrhythmia that cannot be captured using any of the previously described methods in a reasonable time period, invasive electrophysiology testing may be performed to diagnose provocable arrhythmias (eg, VT) or abnormal conducting pathways that do not manifest on the surface ECG. These complex studies are not without risk and are performed only by experienced pediatric cardiac electrophysiologists who have the advantage of performing a highly detailed arrhythmia evaluation

in a controlled setting, testing for short-term drug effects, and also intervening with ablation if needed.

Echocardiography

In the absence of history, symptoms, or physical findings suggestive of underlying heart disease, echocardiography is unlikely to be abnormal. However, it may be helpful for the patient with 1 of these risk factors, and it is recommended for the patient with a high-risk rhythm (eg, VT). Particular emphasis is placed on evaluation of ventricular function. Abnormal contractility may result in arrhythmia, while persistent arrhythmia may result in abnormal contractility.

Cardiac Magnetic Resonance Imaging

In patients with ventricular arrhythmias of unknown etiology, cardiac magnetic resonance imaging may be diagnostic for arrhythmogenic right ventricular cardiomyopathy. Echocardiography is not sensitive for this diagnosis. Cardiac magnetic resonance imaging is also sensitive for fibrosis because of the presence of inflammation in patients with previously undiagnosed myocarditis.

Blood Tests

Many cardiologists screen for thyroid dysfunction in patients with isolated tachyarrhythmias. Doing so is rarely productive, however, particularly in the absence of physical findings such as resting sinus tachycardia, tremor, or sweating. Anemia of at least moderate degree may cause sinus tachycardia or a pounding sensation resulting from high stroke volume; thus, a complete blood cell count may be considered in some cases.

Toxicology Screen

Patients experiencing tachyarrhythmias in an acute setting should be evaluated for possible drug abuse as an underlying cause.

Management

The most common outcome of this type of evaluation is that cardiac arrhythmia is ruled out. When one of the methods of documentation described previously demonstrates normal sinus rhythm during the symptoms, reassurance is all that is needed. Most commonly, pediatric patients evaluated for palpitations have no evidence of cardiac arrythmia and upon monitoring have a normal sinus rhythm. These patients and their families are usually reassured by their normal test results and no further intervention is necessary.

If sinus tachycardia is documented during symptoms, the underlying cause, whether medical or psychosomatic, should be diagnosed and managed appropriately. Minor, clinically insignificant cardiac arrhythmias (eg, isolated low-grade PVCs) usually do not require treatment; reassurance of the patient and parent(s)/guardian(s) is sufficient management.

Several options exist for managing clinically significant cardiac dysrhythmia, and the appropriate method is selected based on the nature of the rhythm and its risk to the patient. Serious ventricular arrhythmias (eg, VT) may require aggressive treatment, such as antiarrhythmic medication, beta blockers, or, in some cases, insertion of an implantable cardioverter-defibrillator. A cardiac electrophysiologist diagnoses VT and initiates the appropriate management.

Supraventricular tachycardia is the most frequently diagnosed clinically significant arrhythmia in children. Beyond the newborn period and in the absence of underlying heart disease, these rhythms are not life-threatening unless they are sustained for very long periods (eg, days), which is uncommon. These rhythms may, however, be quite unpleasant and highly disruptive. The child who experiences infrequent, fleeting episodes of well-tolerated SVT may not require any intervention. However, preexcitation persisting into the second decade may warrant ablation to prevent sudden death in the event of atrial fibrillation. For more troublesome cases, pharmacologic management is usually well tolerated and highly efficacious in preventing recurrences. Currently, results are excellent with interventional catheterization, such as cryoablation or radiofrequency ablation of accessory pathways, and risks to the patient are low. Use of interventional catheterization may enable the child to be free from not only the arrhythmia but also of the need to take daily medications.

In patients with documented SVT, recurrences may result from pharmacologic breakthroughs. In many instances, the recurrence of SVT can be interrupted by use of vagal maneuvers (eg, Valsalva maneuver) or the application of cold water or ice to the face. The use of these maneuvers is not recommended in patients who have not yet had an arrhythmia diagnosis established.

Prognosis

For patients for whom the concern for heart disease is low and for those for whom it is excluded or found not to be clinically significant, the prognosis is the same as for other children. Patients with paroxysmal SVT usually respond well to pharmacologic management, although some experimentation may be necessary to find the best-tolerated and most effective treatment. In the absence of the rare complication of complete heart block, ablative procedures yield an excellent prognosis and often are curative.

The prognosis is less certain for children with serious ventricular arrhythmias, particularly in the setting of arrhythmogenic right ventricular cardiomyopathy, LQTS, or myocarditis. However, the evolution of implantable cardioverter-defibrillators suitable for children has already resulted in improved quantity and quality of life.

CASE RESOLUTION

The child wore a Holter monitor, during which time she was asymptomatic. She was then issued an event detector and 2 weeks later successfully recorded and transmitted her electrocardiogram during an episode of palpitations. It demonstrated SVT at a rate of 250 beats per minute that terminated spontaneously after 20 minutes. Her parents elected to have her undergo electrophysiology study, which demonstrated an aberrant pathway that was successfully ablated without complication. At the 1-year follow-up visit, the patient was free of palpitations, on no medications, and participating actively in age-appropriate activities.

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CHAPTER 103

Cyanosis in the Newborn

Robin Winkler Doroshow, MD, MMS, MEd, FAAP

CASE STUDY

A 3,500-g (7.7-lb) term male neonate born to a 29-year-old, gravida 2 para 2, healthy mother by spontaneous vaginal delivery is well until 24 hours of age, when a nurse notes that he is cyanotic. On examination, he appears blue but in no distress. The vital signs are axillary temperature of 37°C (98.6°F), pulse of 130 beats per minute, respirations of 40 breaths per minute, and blood pressure of 80/60 mm Hg in the right arm. His general appearance is normal except for the cyanosis. His heart sounds are normal, and no murmur is heard. His liver is not palpable, and the peripheral pulses are normal and equal in all extremities. Capillary refill is normal. Oxygen saturation is 65% by pulse oximetry.

Questions

1. What are the causes of cyanosis in newborns?
2. What is the appropriate evaluation of cyanosis in newborns?
3. How urgent is the assessment? What are the risks and benefits of further evaluation?
4. Which aspects of management should be initiated by a primary care physician at a community hospital?
5. Which types of treatment should be undertaken by the consulting pediatric cardiologist at the referral center?

Cyanosis is a bluish appearance of the skin resulting from the presence of reduced hemoglobin in the tissues. Central cyanosis, which is detected initially in the oral mucosa and nail beds but is generalized when severe, indicates at least 4 to 5 g/dL reduced hemoglobin. Hypoxemia is usually the cause. This condition is frequently present in neonates with pulmonary pathology but is also among the most common presentations of severe congenital heart disease (CHD).

Because cyanotic CHD in newborns may be life-threatening, it must not go undiagnosed. Most diagnostic studies have minimal risk. Even the risk of cardiac catheterization, which is rarely indicated, is relatively low in this setting. Most of the lesions that cause cyanotic CHD can be palliated or corrected, and the prognosis is good.

Epidemiology

Cyanotic CHD occurs in approximately 2 to 3 of every 1,000 live births. Approximately 80% to 90% of these patients, usually those that are most severely affected, are detected prenatally or in the first 30 days after birth. Failure to diagnose major cyanotic CHD before newborn discharge, however, occurs in at least 10% of cases, resulting in unnecessary morbidity and mortality. Newborns with low pulmonary blood flow or lesions causing poor mixing most often present with obvious cyanosis, although initially they otherwise appear well and comfortable. Those with high pulmonary flow are less blue and often present first with congestive heart failure (CHF) or a murmur; however, the condition may be detected earlier using screening pulse oximetry.

Although fetal diagnosis continues to improve, most cyanotic CHD is not diagnosed before birth. The antenatal history, gestational age, birth weight, and delivery room examination are unremarkable. Failure to identify CHD in the setting of routine obstetric ultrasonography does not rule it out; the sensitivity of such scans in the general population is very low. Congenital heart disease is more likely in some situations that can be anticipated prenatally (Box 103.1). In these settings, increased suspicion may result in antenatal detection using specialized echocardiography.

Clinical Presentation

Neonates with cyanotic CHD often present within the first week after birth with cyanosis of the oral mucosa. In more severe cases, generalized cyanosis occurs. The abnormal color may be more apparent with effort (eg, feeding, passing stool) or crying. Respiratory distress, which is heralded by grunting, nasal flaring, and retractions, is minor or absent in many newborns with cyanotic CHD; this is in striking contrast to those with respiratory disease, such as respiratory distress syndrome or aspiration pneumonia. In cases of severe hypoxia, metabolic acidosis results in poor perfusion and

Box 103.1. Factors Associated With Increased Risk of Congenital Heart Disease

- Genetic syndromes (eg, trisomies, DiGeorge syndrome)
- Certain extracardiac anomalies (eg, omphalocele, forearm anomalies)
- High incidence of congenital heart disease in the family
- Maternal diabetes if poorly controlled during the first trimester
- Fetal exposure to cardiac teratogen (eg, lithium, isotretinoin)
- Fetal or neonatal arrhythmia other than premature atrial beats

compensatory tachypnea with hyperpnea, a key sign of critical heart disease. Additional findings depend on the nature of the causal lesion (Box 103.2). It is important to note that the absence of associated physical findings does not exclude cyanotic CHD.

Because of the dangers of overlooking ductus-dependent CHD and the suboptimal sensitivity of the physical examination to detect it, all US states (and many other nations) now mandate that newborn screening include pulse oximetry determination(s) prior to discharge, usually at 24 hours of age. This test, often called CCHD (for critical CHD) screening, is a highly sensitive, specific, and cost-efficient means of detecting cyanotic CHD before the cyanosis or other findings become apparent. It allows initiation of intervention (discussed later in this chapter) prior to ductal closure, thereby maintaining the baby's perfusion and oxygenation, and decreasing morbidity and mortality. This approach, which became widespread at the beginning of the 21st century, is likely to become the most common means of diagnosing life-threatening heart disease in the newborn.

For the purposes of this discussion, the term "cyanosis" includes a positive CCHD screen, even if the infant does not appear blue to the naked eye.

Pathophysiology

Cardiac cyanosis is caused by right-to-left shunting so that systemic venous blood bypasses the pulmonary circulation and enters the systemic circulation. Two conditions usually are necessary to produce this type of shunting: a communication (eg, septal defect) for shunting across the blood and a cause (eg, pulmonic stenosis) for shunting away the blood from the lungs. The most notable exception is simple transposition of the great arteries (TGA), in which the fundamental connections are abnormal and all systemic venous blood is directed to the systemic arterial circulation. Lesions associated with cyanosis may be divided into 3 groups: low pulmonary blood flow (LPBF), high pulmonary blood flow (HPBF), and poor mixing.

The *LPBF group* consists of tetralogy of Fallot, pulmonary atresia with intact ventricular septum, and nearly any combination of defects that includes pulmonary atresia or severe pulmonic stenosis. Pulmonary flow is diminished and may derive entirely from the ductus arteriosus while it remains patent. Aside from obvious cyanosis (and associated oxygen saturation <80%), neonates often appear well.

Box 103.2. Diagnosis of Cyanosis in the Newborn: Possible Associated Findings

- Low oxygen saturation
- No improvement with oxygen
- Heart murmur
- Tachypnea
- Increased perspiration
- Abnormal cardiac silhouette on radiograph
- Abnormal electrocardiogram
- Abnormal echocardiogram

The *HPBF group* includes truncus arteriosus, single ventricle, and combinations of defects that involve mixing of oxygenated and unoxygenated blood and little or no obstruction to pulmonary flow. Although a right-to-left shunt is present, the left-to-right shunt is even greater. Pulmonary venous return is therefore voluminous and contributes disproportionately to systemic output. Cyanosis is less apparent; saturation is greater than 80% and may be as high as 95%. Pulmonary flow increases over the first days and weeks after birth as the pulmonary vascular resistance falls and CHF develops, as in patients with isolated shunt lesions (eg, ventricular septal defect). Some neonates with HPBF lesions also have obstruction to systemic blood flow (eg, coarctation of the aorta, hypoplastic left heart syndrome) and may depend on the ductus arteriosus to carry some or all of this flow.

The *poor mixing group* is limited to TGA and its variants. The right and left circuits are in parallel rather than in series, and survival depends on interchange of oxygenated and unoxygenated blood between them. Most newborns with poor mixing present with marked cyanosis (ie, saturation <80%), as with patients in the LPBF group.

Severe hypoxemia (ie, partial pressure of oxygen [PO_2] <35 mm Hg for the average newborn) is not compatible with prolonged survival. Neonates experience tissue hypoxia, anaerobic glycolysis, and metabolic acidosis. Respiratory compensation may occur initially. Even with a normal pH, however, the presence of metabolic acidosis (ie, large base deficit) indicates life-threatening hypoxia, necessitating immediate intervention, without which death ensues in a matter of hours.

Differential Diagnosis

The major causes of cyanosis are cardiac (Box 103.3) and respiratory (Box 103.4). Diagnoses in the latter group include problems of the lung, chest, airway, or respiratory drive.

Persistent fetal circulation, or persistent pulmonary hypertension of the newborn, is perhaps the condition that is most often confused with cyanotic CHD. In this condition the heart and great vessels are structurally normal; however, high pulmonary vascular resistance, which is common in postterm newborns with perinatal distress or pulmonary disease, causes blood to shunt away from

Box 103.3. Cyanotic Congenital Heart Defects

Low Pulmonary Blood-flow Lesions

- Tetralogy of Fallot
- Pulmonary atresia with intact ventricular septum
- Complex lesions with severe pulmonary stenosis or atresia
- Obstructed total anomalous pulmonary venous return

High Pulmonary Blood-flow Lesions With Mixing

- Truncus arteriosus communis
- Tricuspid atresia
- Transposition with ventricular septal defect

Poor Mixing (ie, Transposition of the Great Arteries)

Box 103.4. Noncardiac Causes of Neonatal Cyanosis

- Persistent fetal circulation
- Upper airway obstruction (eg, choanal atresia)
- Pulmonary infection (eg, group B streptococcal infection)
- Aspiration (eg, meconium aspiration syndrome, tracheoesophageal fistula)
- Pulmonary hypoplasia (eg, Potter syndrome, diaphragmatic hernia)
- Respiratory distress syndrome (eg, in preterm neonates)
- Thoracic hypoplasia (eg, thanatophoric dwarfism)
- Hypoventilation (eg, neurologic depression)

the lungs at the foramen ovale and ductus arteriosus. Profound cyanosis that is unresponsive to supplemental oxygen, particularly in postductal sites (eg, lower extremities), may be the only abnormal finding, and echocardiography is required to exclude CHD.

Pulmonary cyanosis may be caused by infection (eg, group B streptococcal pneumonia); aspiration (eg, meconium, tracheoesophageal fistula); pulmonary hypoplasia (eg, oligohydramnios sequence, diaphragmatic hernia); respiratory distress syndrome (eg, preterm); or a host of other problems of the lung, chest, or airway. Neurologic depression may produce hypoventilation with resultant hypoxia.

Evaluation

Evaluation of the newborn with cyanosis must be expeditious so that management is not delayed. In some cases, therapy may be initiated before the evaluation is complete. All available data, including the statistical likelihood of CHD and the risk-benefit ratio of the treatment, must be considered.

History

Review of the history may be helpful, particularly in certain situations, such as in newborns with pulmonary disease (Box 103.5). It is important to note that a negative response to any or all of the questions does not render cyanotic CHD unlikely; in fact, negative responses are noted in most patients with cyanotic CHD.

Box 103.5. What to Ask

Newborn With Cyanosis

- Has the neonate been in any distress?
- Has the neonate had difficulty feeding?
- Was the neonate suspected of having a heart problem prenatally (eg, fetal arrhythmia, abnormal heart on ultrasonography)?
- Does the mother have diabetes?
- Did the mother take any drugs—prescribed or not—during the pregnancy?
- Was the mother ill during the first trimester?
- Is there a positive family history of congenital heart disease or other birth defects?
- Did any perinatal problems occur (eg, passage of meconium in utero)?

Physical Examination

Peripheral cyanosis, also known as acrocyanosis, involves the extremities and the circumoral area. This is a normal finding in newborns and does not reflect the arterial desaturation of cyanotic CHD. Central cyanosis involves the oral mucosa but may be generalized. It may be the only abnormal physical finding in cardiac patients; however, a careful, thorough examination often yields information about the underlying cardiac defect and overall circulatory status. External anomalies or abnormal phenotypic appearance may be indicative of a genetic disorder with associated cardiac anomalies. Dyspnea (eg, grunting, nasal flaring, intercostal retractions) is more common with lung disease, but tachypnea (ie, rapid respiration) is common with severe heart disease and pulmonary problems. Tachypnea results from CHF in the setting of HPBF lesions and hyperpnea (ie, deep breathing) resulting from metabolic acidosis in patients with severe hypoxia or impaired perfusion. Poor perfusion is also manifested by abnormal color (ie, a gray or ashen appearance if combined with cyanosis), cool extremities, delayed capillary refill, and diminished pulses.

The peripheral pulses must be palpated in all extremities. Abnormalities or discrepancies between extremities should be confirmed by measuring blood pressures. Weak pulses may occur in the setting of cardiogenic shock, and bounding pulses may be noted with diastolic runoff lesions, such as patent ductus arteriosus or aortic insufficiency. Pulse quality and blood pressure may differ between extremities if an aortic arch abnormality, such as coarctation, is present. The abdominal examination may reveal hepatomegaly in patients with CHF; alternatively, it may reveal abnormal situs, as in Ivemark syndrome, which usually is associated with complex cyanotic CHD.

The cardiac examination may disclose a loud murmur if an obstruction such as pulmonary stenosis is present. The examiner should note, however, that atresia—a total obstruction—produces no murmur. Heart sounds may be loud and the precordium hyperdynamic, particularly in newborns with HPBF. Splitting of the second heart sound confirms the presence of 2 patent semilunar valves; however, this finding is often difficult to appreciate even in healthy newborns.

Laboratory Tests

Several laboratory studies are available for evaluating congenital heart disease (see Chapter 104, Table 104.1). As in CHF, initially it is more important to determine whether the patient has heart disease than to obtain a precise, complete diagnosis. In cyanotic CHD, sophisticated studies such as echocardiography, magnetic resonance imaging, and catheterization usually are necessary to make a detailed diagnosis.

The suspicion of arterial hypoxemia should be confirmed by pulse oximetry, an indirect measurement. This method is readily available and noninvasive but has shortcomings. Perfusion must be adequate to obtain a reading. Accuracy is diminished at saturations below 75%, although the presence of profound hypoxia can still be

confirmed. Cyanotic CHD cannot be ruled out by pulse oximetry, however, because readings of 100% saturation may reflect PO_2 values ranging between 75 and 250 mm Hg (Figure 103.1). Arterial blood gases are more accurate than pulse oximetry and provide important additional information about ventilation and acid-base status. Arterialized capillary gases may suffice if perfusion is adequate.

Oxygenation may differ between the extremities in newborns with certain lesions (eg, coarctation). The site of sampling should be noted. If possible, the saturation should be measured at sites proximal and distal to the ductus arteriosus (ie, the right arm and either leg).

A shunt study, also known as a hyperoxia challenge, may be performed to determine whether a right-to-left cardiac shunt is present, particularly if echocardiography is not readily available. Pure oxygen (fraction of inspired oxygen in gas [FiO_2] = 1.00) is given for 5 to 10 minutes by hood. In patients with LPBF or TGA, increasing the inspired oxygen does not affect the oxygenation of the blood because the blood cannot enter the lungs; this is a positive result. In patients with pulmonary disease or hypoventilation, oxygenation increases strikingly, often to a PO_2 exceeding 200 mm Hg; this negative result rules out cyanotic CHD.

A blunted shunt study, which is characterized by a rise in PO_2 but rarely to levels above 150 mm Hg, is seen in patients with severe pulmonary disease and in those with HPBF lesions. With such lesions the pulmonary venous blood is high in volume, and the rise in its saturation causes a definite rise in arterial oxygenation. This effect is exaggerated by the further increase in pulmonary flow resulting from the vasodilating effect of oxygen.

A positive shunt study may be identified with pulse oximetry. It is difficult or impossible, however, to distinguish between a blunted study and a negative study with this tool. The oxyhemoglobin dissociation curve is flattened at the upper end, and the saturation changes very little over a wide range of PO_2 (Figure 103.2). Although capillary gases may be equally inaccurate in this range, directly measured arterial blood gases are highly reliable. Additionally, they may reveal hypercapnia, with or without respiratory acidosis, which is suggestive of a pulmonary cause for the hypoxia.

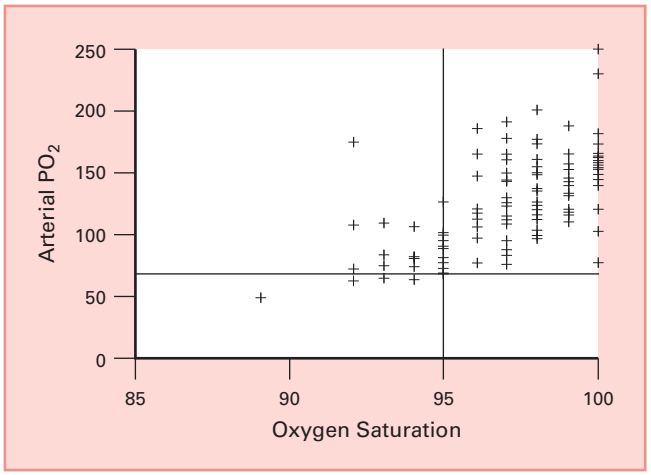

Figure 103.1. Comparison between partial pressure of oxygen (PO_2) by arterial blood gas measurement and oxygen saturation by pulse oximetry.
Reproduced with permission from Niehoff J, DelGuercio C, LaMorte W, et al. Efficacy of pulse oximetry and capnometry in postoperative ventilatory weaning. *Crit Care Med.* 1988;16[7]:701–705.

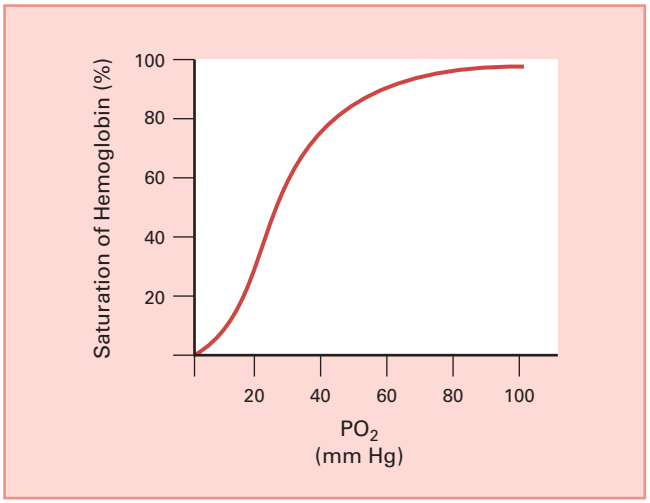

Figure 103.2. Oxyhemoglobin dissociation curve. Note that the position of the curve itself may vary with temperature, pH, partial pressure of oxygen (PO_2), and 2,3-diphosphoglycerate.

Electrocardiography (ECG) is a relatively inexpensive, readily available noninvasive test. It does not often help distinguish cyanotic CHD from other causes of cyanosis, however, particularly for those health professionals who lack experience with neonatal ECG. The normal range is large in neonates, with much overlap between normal and CHD. Care must be taken in correctly placing the leads and minimizing artifacts; incorrect technique may elicit a false-positive result.

Imaging Studies

Chest radiography is a relatively inexpensive and readily available test that often is extremely helpful in differentiating between cardiac and noncardiac disease. Pulmonary disease is often readily apparent on chest radiography. This test also helps define the cardiac diagnosis broadly but not precisely. Patients with LPBF lesions have small hearts and diminished pulmonary blood flow. In contrast, patients with HPBF lesions have large hearts and increased flow, such as is seen in neonates with simple left-to-right shunts. With many cyanotic lesions, the cardiac silhouette is abnormal in configuration (eg, boot-shaped heart in tetralogy of Fallot) or position (eg, dextrocardia in patients with heterotaxy syndrome), but this finding may be obscured by the generous thymus in the newborn. Transposition of the great arteries may be more misleading; pulmonary flow may be increased despite the severe cyanosis, and the heart size may be normal. An apparently normal radiograph does not exclude TGA.

Under optimal conditions, echocardiography enables the physician not only to recognize CHD but to identify details of anatomy and physiology. Conversely, a properly performed, complete, negative echocardiogram rules out CHD. The performance of a high-quality study requires the appropriate equipment (with high-resolution imaging), an experienced sonographer, and an experienced cardiologist for interpretation. In the absence of these elements, preliminary

echocardiography, such as bedside limited echocardiography by the emergency physician, may be used cautiously as a screening device as part of the initial assessment to confirm the presence of heart disease before referral to a specialist. It is not, however, of adequate sensitivity to rule out some life-threatening congenital heart defects, such as anomalous drainage of pulmonary veins or anomalous origin of coronary arteries. Recently, availability of telemedicine for echocardiography has helped fill this gap in some hospitals and avoid some unnecessary transports. When significant suspicion exists for cyanotic CHD, the patient should be referred even if echocardiography has not yet been performed.

Management

Initial management prior to cardiac consultation (often with transfer to another institution) includes surveillance, assistance, supportive care, and direct medical management.

Close surveillance, including transfer to the highest level of neonatal care available, use of a cardiopulmonary monitor and continuous pulse oximetry, frequent monitoring of vital signs, and repeat physical examinations, is begun as soon as cyanotic CHD is identified. Even if the newborn is feeding well, it is best to suspend feedings because of the likelihood of spontaneous deterioration and the emergent need for invasive procedures. An orogastric tube is placed to decompress the stomach, reducing the work of breathing as well as the risk of aspiration. At least 1 secure intravenous line should be placed for administration of fluids, glucose, and medications. Expeditious establishment of umbilical arterial catheterization allows close monitoring of arterial blood gases and blood pressure. The latter may be difficult to measure by cuff in the compromised newborn.

While undertaking these measures, the physician should make every effort to seek assistance from a pediatric cardiologist. A neonatologist may be consulted if a pediatric cardiologist is not immediately available. Much advice may be obtained by telephone. Additionally, plans for immediate consultation or transfer of patients may be discussed in this way.

The need for supportive care depends on the case. In the absence of metabolic acidosis or impaired perfusion, no special measures are indicated in this category. In some cases, intravenous fluid boluses, inotropic agents, and other treatments may be necessary as part of early management. Mechanical ventilation should be used in patients with metabolic acidosis, whether compensated or uncompensated, because of the increased oxygen requirement produced by hyperventilation and the tendency for tiring, resulting in superimposed respiratory acidosis.

The temptation to give supplemental oxygen for more than the few minutes necessary to perform a shunt study is great but must be resisted. Oxygen is rarely helpful and may be harmful in this setting. In neonates with TGA or LPBF lesions, oxygenation is not affected. In newborns with HPBF lesions, oxygenation is usually adequate in room air (saturation >80%), and an increase in FiO_2 may exacerbate CHF. Patients at greatest risk for deterioration resulting from administration of oxygen are those with total anomalous pulmonary venous return with obstruction, in whom pulmonary arteriolar vasodilation precipitates severe pulmonary edema and secondary right heart failure. Oxygen may also directly constrict the ductus arteriosus on which the cyanotic newborn may depend.

The possibility of ductal dependency should prompt consideration of administering the ductus dilator, prostaglandin E1 (PGE_1). This lifesaving treatment may be started before definitive diagnosis of cyanotic CHD. In newborns who remain adequately oxygenated (ie, no acidosis) and perfused, the drug can be prepared but administration deferred pending consultation. The benefits of giving PGE_1 to neonates with severe hypoxia or compromised perfusion far outweigh the risks, which include apnea and fever. A dramatic improvement often occurs within seconds to minutes, which supports the diagnosis of a ductal-dependent lesion and enables the physician to stabilize the patient until more definitive evaluation and intervention can take place.

Prognosis

If untreated, LPBF lesions and TGA are usually fatal during infancy, most often during the neonatal period, because of severe hypoxia. Untreated HPBF lesions may result in death in infancy from CHF or complications, such as pneumonia. If the systemic blood flow is ductus dependent (eg, interruption of the aortic arch), death occurs shortly after ductal closure, usually during the first week after birth. Even when the outcome is not fatal, delayed diagnosis may result in a suboptimal outcome, including end-organ injury, such as renal dysfunction or neurologic sequelae.

With early recognition and intervention, however, the prognosis for newborns with cyanotic CHD is surprisingly good in the absence of a genetic syndrome (eg, trisomy 18) or a major complicating extracardiac malformation (eg, neural tube defect). If neonates are diagnosed before the onset of severe circulatory compromise, they can be stabilized and evaluated promptly, and palliative or corrective procedures can be performed in the operating suite or catheterization laboratory. Most of these patients survive well into adulthood with a good quality of life. Newborns with lesions in which all 4 chambers are adequate in size (eg, tetralogy of Fallot) have a better lifetime prognosis than those with a hypoplastic chamber (eg, tricuspid atresia). Currently, even neonates with abnormalities such as Ivemark syndrome (ie, asplenia syndrome) or hypoplastic left heart syndrome have a reasonable outlook with complex staged reconstructive surgery or heart transplantation.

CASE RESOLUTION

Marked hypoxia is present in the absence of other cardiac findings, such as a heart murmur. The oxygen saturation does not rise after the newborn breathes 100% oxygen for 10 minutes. The chest radiograph shows a small, boot-shaped heart and diminished pulmonary blood flow, and ECG is normal. Transport is arranged. Because of the marked cyanosis, infusion of PGE_1 is begun, and saturation increases to 80%, with the PO_2 rising from 33 mm Hg to a safer 48 mm Hg. The neonate is transferred to a tertiary care center, where consultation is obtained. Echocardiography is also performed, which demonstrates tetralogy of Fallot with pulmonary atresia. A modified Blalock-Taussig shunt is placed in the newborn period, and complete repair using a pulmonary artery homograft is performed at 1 year of age.

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CHAPTER 104

Congestive Heart Failure

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CASE STUDY

A 2-month-old boy is brought to the office by his mother, who reports that her son has been eating poorly and breathing oddly for the past few days. The perinatal history is unremarkable. A heart murmur was noted at the 1-month checkup.

The infant is quite thin and irritable. Physical examination shows that the baby's weight, which was at the 50th percentile at birth, is now at the fifth percentile; his height, which was at the 50th percentile, is now at the 25th percentile. He is afebrile, and his heart rate is 165 beats per minute, with respirations 70 breaths per minute and shallow but without respiratory distress. The skin is pale and diaphoretic, and the mucous membranes are pink. Examination of the head and neck is normal; no jugular distention is present. The lungs are clear. The precordium is hyperdynamic, and the heart sounds are loud; a prominent systolic murmur is audible at the left lower sternal border. The liver edge is palpable 4 cm below the right costal margin in the right midclavicular line, and the spleen is not palpable. The extremities are thin, with normal pulses and no edema. Capillary refill is slightly delayed.

Questions

1. What are the signs of cardiac disease in infants and children?
2. What are the signs of congestive heart failure in children? How do these signs in children differ from those in adults?
3. What underlying disorders can cause congestive heart failure in young infants?
4. What is the appropriate emergent treatment for infants with congestive heart failure?

Congestive heart failure (CHF) is the most common symptomatic presentation of serious heart disease in infants. Although this condition also occurs in older children, an estimated 90% of cases of CHF in the pediatric population begin in the first year after birth. In infants and young children, CHF is most often caused by structural congenital heart disease (CHD); in older children, acquired cardiomyopathy and myocarditis are more prevalent. Compensatory mechanisms are fewer and less successful in small infants. Other causes of CHF are included in Box 104.1.

Epidemiology

The prevalence of CHF in children is approximately 0.1%. Most cases result from CHD, which occurs in 0.8% of live births. Each year, approximately 14,000 pediatric patients are hospitalized for management of CHF in the United States. The prevalence of CHD varies little by geography, ethnic group, or sex, but it is much more common in children with recognizable genetic syndromes (eg, Down syndrome, Turner syndrome). Rheumatic fever, which is far more prevalent in developing countries, is a rare cause of CHF in the United States.

Clinical Presentation

Most commonly, initial symptoms of CHF in an infant take the form of parental concerns about feeding. Comments are often vague (eg, "My baby is not a good eater") but may be more precise (eg, "He is taking less formula with each feeding"; "He is taking longer to nurse"). The parent or caregiver may also describe rapid breathing, excessive sweating, or decreased activity, but usually only on specific questioning. The older child with CHF may report subjective symptoms, such as shortness of breath.

Box 104.1. Causes of Congestive Heart Failure in Children

Volume Overload
- Left-to-right shunt (eg, ventricular septal defect)
- Bidirectional shunt (eg, truncus arteriosus)
- Valvar insufficiency (eg, mitral regurgitation)
- Extracardiac conditions (eg, anemia, arteriovenous malformation)

Pressure Overload
- Outflow obstruction (eg, coarctation of aorta)
- Inflow obstruction (eg, obstructed anomalous pulmonary veins)
- Vascular resistance (eg, hypertension, chronic obstructive pulmonary disease)

Myocardial Dysfunction
- Intrinsic conditions (eg, cardiomyopathy, anthracycline toxicity)
- Inflammatory conditions (eg, viral myocarditis, rheumatic fever)
- Coronary insufficiency (eg, anomalous left coronary artery)

Arrhythmias
- Tachyarrhythmia (eg, paroxysmal supraventricular tachycardia)
- Bradyarrhythmia (eg, third-degree atrioventricular block)

Congestive heart failure may also be detected on examination during routine infant checkups or evaluations for non-cardiac symptoms. In the child with CHF, careful assessment of the physical findings, including vital signs, reveals tachypnea, tachycardia, and hepatomegaly and often signs of underlying structural heart defects, such as a murmur (Box 104.2).

Pathophysiology

High cardiac output may result in CHF in the infant with a large left-to-right shunt. Myocardial contractility is relatively normal, and the child remains on the "normal" line of the Starling curve, which relates cardiac output to diastolic volume (also called *preload)* or pressure (Figure 104.1). The shunt requires a very large volume of output, primarily to the pulmonary bed. Although the heart may be able to meet this demand, preload is high, resulting in "congestive" signs and symptoms (eg, tachypnea, hepatomegaly). In more severe cases, systemic output may be compromised, resulting in hypotension, decreased systemic perfusion, renal failure, and metabolic acidosis.

Left-sided failure resulting in elevated pulmonary venous pressure produces increased lung water. Initially, this fluid is interstitial, and it does not interfere with gas exchange but does trigger reflex tachypnea. Minute volume is kept normal by decreasing tidal (ie, breath-to-breath) volume, resulting in shallow, rapid breathing (sometimes called "happy tachypnea" because of the absence of dyspnea). Only when the ability of the pulmonary lymphatics to drain this fluid is overcome by large volume does fluid accumulate in the alveoli; rales and respiratory distress, or dyspnea, result and gas exchange may be compromised.

Right-sided failure caused by an elevated systemic venous load usually produces more volume than pressure load on this system, possibly as a result of the greater venous compliance in infants compared with adults. The liver becomes quite distended and is easily palpated. As long as the liver can absorb the increased venous volume, the portal pressure does not rise, and splenomegaly does not occur. Because the venous pressure rises very little, jugular distention, which is always difficult to detect in the young infant, rarely occurs; edema is also rare.

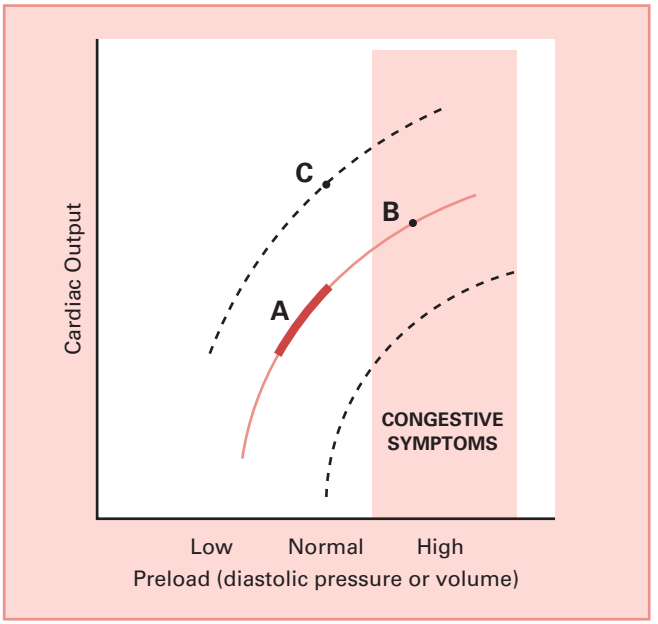

Figure 104.1. Relationship of cardiac output to preload. The solid curve represents normal myocardial contractility, and the dotted curves represent impaired function (shifted downward) and the positive inotropic state (shifted upward). A, Normal range (no heart disease). B, Left-to-right shunt with congestive heart failure (CHF). Note that overall output is high, but most of it is shunted. C, Same situation as B but after treatment for CHF. Cardiac output is the same or better, but preload is now out of the range that results in congestive symptoms.

Box 104.2. Diagnosis of Congestive Heart Failure in the Pediatric Patient

Infants and Toddlers

- Tachycardia
- Tachypnea
- Hepatomegaly
- Sweating
- Decreased feeding
- Irritability
- Easy fatigability
- Poor weight gain

Older Children

- Shortness of breath
- Exercise intolerance
- Peripheral edema
- Abdominal discomfort (eg, hepatomegaly)
- Orthopnea

The left and right (ie, systemic and pulmonary, respectively) circulations are more interdependent in infants and younger children than in older children and adults. As a result, in infants and younger children bilateral heart failure is much more common than right-sided or left-sided failure alone. Although this means that recognition of CHF may be easier in younger patients, determination of the underlying condition may be more difficult because the clues are less specific. For example, in an adult with left-sided failure, the differential diagnosis includes mitral, but not tricuspid, valve disease.

Differential Diagnosis

In the presence of tachycardia, tachypnea without dyspnea, and hepatomegaly, the diagnosis of CHF is straightforward. Congestive heart failure is most commonly confused with major respiratory infections, such as bronchiolitis and pneumonia. Pulmonary infections frequently are associated with dyspnea as well as tachypnea, impaired gas exchange, and other respiratory findings. Rhinorrhea, cough, fever, or wheezing may also be present. Rales may accompany pneumonia but are rare in CHF of infancy or early childhood. Hyperinflation caused by lung disease may result in a false

impression of hepatomegaly. In some children, CHD, CHF, and respiratory infections coexist and compound one another to increase morbidity and mortality, as is seen with respiratory syncytial virus.

Signs of structural heart disease, such as a murmur or absent femoral pulses, may support the diagnosis of CHF. Severe CHF, with low cardiac output or even shock, has a broader differential diagnosis. In addition to cardiac causes, sepsis, hypovolemia, and disorders associated with inborn errors of metabolism should be considered.

Evaluation

History

The history should include specific questions about feeding and growth (Box 104.3). Poor feeding, which is often a nonspecific symptom in infants with chronic or subacute illness, results from tachypnea and fatigability in infants with heart disease. Growth failure may result from poor feeding and increased cardiopulmonary work. The physician should specifically query the parent or caregiver about possible excessive sweating or rapid breathing in infants, because that information may not be volunteered.

Physical Examination

The diagnosis of CHF is primarily based on clinical findings, and physical examination is essential. The resting respiratory rate must be precisely counted, because the infant with CHF most often exhibits tachypnea without dyspnea. The liver edge is palpable more than 1 cm below the right costal margin in the midclavicular line, and the extent of enlargement mirrors the severity of the CHF.

The physical examination may also provide clues about the underlying cause of CHF, such as a heart murmur or gallop, or pulses that are weaker in the lower extremities than the upper extremities.

In the older child or adolescent, physical findings are more similar to those of the adult with CHF. Additional findings that may be present in the older child or adolescent include jugular venous distention, basilar rales, and peripheral pitting edema.

Box 104.3. What to Ask

Congestive Heart Failure

Infants

- How has the infant been feeding? Does the infant get out of breath or appear exhausted?
- Has the infant's growth pattern changed recently?
- Does the infant tire easily? With eating?
- Does the infant perspire excessively, especially with efforts such as feeding?
- Does the infant breathe rapidly, even at rest?

Children

- Has a significant change in exercise capacity occurred?
- Has any significant weight loss or weight gain occurred?
- Have there been any episodes of atypical syncope? Palpitations?
- Is there any family history of cardiomyopathy or heart transplantation?

In infants and children with severe CHF, in whom cardiac output is declining, flow to end organs is compromised. The skin is cool and pale or ashen, and capillary refill is delayed; additionally, the peripheral pulses are diminished. Mental status may be affected, resulting in lethargy or even unresponsiveness (see Chapter 74).

Diagnostic Studies

Many diagnostic studies can be performed to assess the heart, including electrocardiography and echocardiography (Table 104.1). Some procedures are quite costly, however, and some are invasive and therefore carry risk. The value of most of these tests depends

Table 104.1. Diagnostic Studies Used in the Evaluation of Heart Disease in the Pediatric Patient

Test	*Information*
Chest radiography	Presence and direction of shunt Hints concerning specific diagnosis (and possible pulmonary disease ruled out)
Serum BNP or NT-proBNP	Presence and severity of congestive heart failure
ECG	Cardiac rhythm and conduction Chamber overload Coronary insufficiency
Ambulatory ECG	Subacute rhythm assessment Correlation of symptoms with rhythm
Oximetry	Presence and severity of hypoxemia
Arterial blood gases	Hypoxemia Acid-base status
Hematocrit	Anemia Polycythemia
Troponins; CK MB	Presence and acuteness of myocardial injury or ischemia
Exercise test	Quantitation of exercise tolerance Provocation of symptoms or arrhythmia
Echocardiography	Specific structural diagnosis and hemodynamics Chamber enlargement and systolic and diastolic function Presence of pericardial effusion
Cardiac magnetic resonance imaging or computed tomography	Specific structural diagnosis and hemodynamics Chamber enlargement and function
Cardiac catheterization	Specific structural diagnosis and hemodynamics Cardiac electrophysiology
Tilt test	Autonomic function

Abbreviations: BNP, brain natriuretic peptide; CK MB, creatine kinase enzyme (1 of 3 forms of creatine kinase) found primarily in heart and skeletal muscle cells; ECG, electrocardiography; NT-pro BNP, N-terminal pro–brain natriuretic peptide.

on the expertise of the individuals who perform and interpret them. It is important to remember that although test results and consultation with a pediatric cardiologist may be invaluable in the identification of the underlying lesion, these procedures usually are not required to make a diagnosis of CHF.

Pressure or volume overload of the ventricles causes them to release the neurohumoral peptide brain natriuretic peptide (BNP), which acts as a natural natriuretic, diuretic, and vasodilator. Studies in adults have demonstrated that blood levels of BNP and its more stable precursor, N-terminal proBNP (NT-proBNP) are elevated in CHF, and the degree of elevation closely reflects severity of CHF. This test, which may be performed at the bedside on very small samples of blood, may be used to distinguish between CHF and other similar disorders, such as acute pulmonary disease. Because it closely parallels changes in severity of CHF, this test may also be used to track response to treatment. Recent studies in children suggest that the test may be similarly useful in the pediatric population.

In the child with severe CHF, further studies are indicated. Arterial blood gases show evidence of metabolic acidosis resulting from tissue anoxia, with respiratory compensation in early stages and superimposed respiratory acidosis in later stages. A complete blood cell count shows leukocytosis caused by stress. It may not differentiate between heart disease and sepsis, however (Figure 104.2).

Imaging Studies

Because elucidation of the structure and function of the heart is central to assessment of the underlying cause of CHF in the pediatric population, imaging studies play a key role in evaluation of these patients. Moreover, these tests (particularly echocardiography) may be used as a means of tracking response to treatment. The echocardiogram may provide clues to the underlying pathology but does not aid in the diagnosis of CHF.

Chest radiography, preferably the anteroposterior and lateral views, may be quite useful as a supportive study. It may show cardiomegaly, pulmonary venous congestion, and hyperinflation. Cardiomegaly is most commonly caused not by myocardial dysfunction but by volume overload from the shunt. In the absence of cardiac enlargement, the diagnosis of CHF must be seriously questioned. (However, CHF may occur in the absence of cardiomegaly in total anomalous pulmonary venous return with obstruction, which usually presents in the first week after birth in association with hypoxia.) Pulmonary venous congestion occurs in left-sided heart failure, but increased pulmonary arterial flow from a left-to-right shunt often obscures the congestion. Hyperinflation resulting from peribronchial edema is also a common finding.

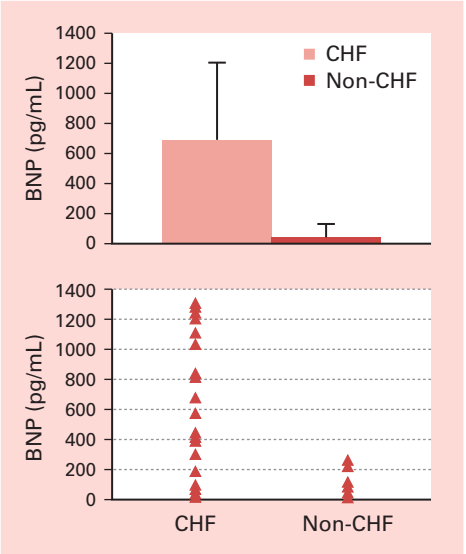

Figure 104.2. Utility of brain natriuretic peptide (BNP) in differentiating congestive heart failure (CHF) from lung disease in pediatric patients with respiratory distress.

Adapted from Koulouri S, Acherman RJ, Wong PC, Chan LS, Lewis AB. Utility of B-type natriuretic peptide in differentiating congestive heart failure from lung disease in pediatric patients with respiratory distress. *Pediatr Cardiol.* 2004;25[4]:341–346, with permission from Springer Science + Business Media.

Management

All infants and children with CHF should be under the care of a pediatric cardiologist, often in concert with a pediatrician, intensivist, or neonatologist. Prompt referral to a cardiologist aids not only in management of the CHF but also in assessment and management of the underlying disorder.

Most evidence about management of CHF derives from studies conducted in adults, whose etiology (eg, ischemic heart disease) and pathophysiology are quite different from those in most pediatric patients with CHF. Additionally, the numbers of pediatric patients with CHF are significantly lower and therefore do not lend themselves to statistically meaningful clinical trials. The heterogeneity of causes in children also contributes to this obstacle.

The pharmacologic treatments for pediatric CHF fall into a small number of categories based on mechanism of action (Table 104.2). Preload can be optimized by the administration of diuretics and vasodilators, and afterload can be optimized by the use of arteriolar dilators, some of which also have inotropic effects. Contractility is enhanced by inotropic agents, and antiarrhythmics control tachycardia and bradycardia to optimize heart rate. The most effective control of CHF is attained when more than 1 mechanism is used.

Inotropes and diuretics are used in the initial management of CHF in children. Inotropic support results in a shift to a higher Starling curve (Figure 104.1), which allows affected patients to maintain the high volume output necessitated by the underlying CHD at lower diastolic pressures, thus alleviating congestive symptoms. Digoxin, a form of digitalis, is commonly used when cardiac output is not severely impaired and is therefore often used in outpatients. This agent is readily available, consistently absorbed, safe in the therapeutic range, and easy to administer orally. If digoxin is initially given at the maintenance dose (10 mcg/kg/day), therapeutic levels are not attained for approximately 1 week; therefore, loading is preferable but may require hospitalization. Digoxin is well tolerated and rarely causes side effects. Because of its safety and reliability of absorption, blood levels need not be checked unless overdose is suspected (eg, history

Table 104.2. Therapy for Pediatric Congestive Heart Failure

Disease Severity	*Therapy Type*	*Example*
Chronic (ambulatory)	Cardiac glycosides	Digoxin
	Diuretics	Furosemide, spironolactone
	Angiotensin-converting enzyme inhibitors	Enalapril, captopril
	Angiotensin receptor blockers	Losartan potassium
	Selective beta blockers	Carvedilol, metoprolol
Acute (inpatient)	Diuretics	Furosemide, bumetanide
	β agonists	Dobutamine, dopamine
	Phosphodiesterase inhibitors	Milrinone, amrinone
	Vasodilators	Nitroprusside, oxygen, inhaled nitric oxide
Severe, Refractory	Mechanical support	Extracorporeal membrane oxygenation, ventricular assist
	Organ replacement	Cardiac or cardiopulmonary transplantation
	Exogenous brain natriuretic peptide	Nesiritide

of over-administration, toxic ingestion, unexplained vomiting, second- or third-degree heart block). In the neonate, blood levels may be difficult to interpret because of the presence of natural digoxin-like immunoreactive substance in the blood.

The elevated diastolic preload of CHF is the result of neurohumorally mediated sodium and water retention. Diuretics reverse this phenomenon. Furosemide, a potent loop diuretic that is available in an oral suspension and is fairly well absorbed, is the most frequent drug of choice for the outpatient. Initially, furosemide may be given intravenously or intramuscularly rather than orally, which reduces the time to onset of action and is more effective. Such treatment also supports the patient while digoxin loading is in progress. Spironolactone, a less potent diuretic, may be used in combination with furosemide for its potassium-sparing effects and may also reduce the deleterious histopathologic and structural changes known as *myocardial remodeling* that can accompany CHF.

Fluid and sodium restriction, which is often used in adults with CHF, is difficult to achieve with infants because of their predominantly or exclusively liquid diet. High-calorie diets using concentrated formulas, complex carbohydrate additives, or medium-chain triglyceride oils may reduce the intake of free water and the effort of feeding without compromising caloric intake. In older infants and children with CHF, salt intake is more easily modified and should be minimized.

Certain pediatric patients with chronic CHF may benefit from the addition of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to their regimen. These arteriolar dilators help control afterload and have been shown to be effective in children with dilated cardiomyopathy and those with a large left-to-right shunt, such as ventricular septal defect (VSD). Recent observations suggest that third-generation beta blockers, such as carvedilol, may be useful to control chronic CHF in children with dilated cardiomyopathy. Randomized, controlled clinical trials in adults with similar pathology have been quite encouraging, despite poor understanding of the mechanism involved; similar trials in children have thus far been disappointing.

The child with acute, severe, or refractory CHF may require additional medications or interventions, necessitating hospitalization, often in an intensive care unit. These therapies include β agonists and phosphodiesterase inhibitors for inotropic support and vasodilators for afterload reduction, correction of anemia (eg, transfusion), treatment of fever (eg, antipyretics), and reduction of metabolic demands (eg, ventilatory support, bed rest, sedation). Diuretics, usually given intravenously, provide effective control of congestive symptoms. Because of the importance of fluid balance and nutrition in the child hospitalized with CHF, close and accurate monitoring of fluid intake and output, measurement of daily weight, and measurements of serum electrolytes are essential data in the management of CHF. Feeding is often problematic because of its increased workload, conflict with the increased work of breathing, and diminished circulation to the gut. In some cases, tube feedings may be an option; in others, all enteric feedings must be discontinued and hydration and nutrition maintained intravenously.

In a minority of cases, CHF is refractory to all these measures. This may occur with very severe acute myocarditis, with long-standing cardiomyopathy of various causes, and during the postoperative period after complex CHD surgery. Additional options include *resynchronization therapy*, in which an artificial pacemaker alters the sequence of ventricular depolarization and contraction, and mechanical support, such as extracorporeal membrane oxygenation and ventricular assist devices. Exogenous recombinant BNP (ie, nesiritide), which has shown some promise in the setting of adult CHF, may be helpful. In some cases, replacement of the ailing heart or heart-lung unit by transplantation may be the only remaining alternative.

Ultimately, the best management for pediatric CHF is often treatment of the underlying disorder. In many instances, failure to do so results in limited or no success of other treatment modalities. The degree of urgency depends on the nature of the disorder and the severity of the CHF. For example, in the neonate with a ductus-dependent lesion, such as hypoplastic left heart syndrome, maintenance of ductal patency with prostaglandin E_1 is crucial to initial management. In the infant with CHF caused by supraventricular tachycardia, prompt conversion to normal sinus rhythm is often the only treatment necessary. Congestive heart failure caused by severe anemia responds dramatically to correction of hemoglobin levels, often using exchange transfusion to avoid additional acute volume overload. Cor pulmonale, which occurs in children with severe chronic lung disease, is most responsive to measures directed at improving the lung disease or decreasing pulmonary vascular resistance (eg, supplemental oxygen, inhaled nitric oxide),

or systemically administered pulmonary vasodilators (eg, sildenafil citrate). Congestive heart failure caused by structural CHD (the most common situation) typically can be reversed with surgery or interventional catheterization to palliate the problem (eg, pulmonary artery banding in certain cases with large net left-to-right shunts) or correct the defect (eg, repair of VSD). It is rarely necessary to "tolerate" prolonged, uncontrolled CHF in children or to manage the condition aggressively at the expense of a major change in lifestyle.

Family counseling is essential and should begin when CHF is identified. In addition to providing a general description of the cardiac defect and CHF, the physician must take care to make several additional points and clarifications. The meaning of the term *heart failure,* which is commonly thought by nonmedical professionals to refer to a sudden deterioration of heart function or even cardiac arrest, must be clarified. It is also important to stress that the affected infant should be treated as normally as possible, with the exception of administration of medicines and keeping medical appointments. Contrary to popular belief, most infants with cardiac conditions are not fragile. Addressing quality-of-life issues, such as parental or caregiver concern, assuaging guilt, and normalizing existence, are key responsibilities of the medical professional.

Prognosis

In most young infants and children with CHF, the prognosis is excellent. Congestive heart failure responds well to treatment, and the underlying defect usually can be corrected or at least palliated. "Catch-up" growth occurs with remission of CHF, and children have the potential to reach their genetically determined height and weight. Without cardiac surgery for CHD, CHF often remits spontaneously over months or years as a result of positive developments, such as maturation of compensatory mechanisms or spontaneous improvement in the defect (eg, decrease in the size of a VSD), or as a result of negative developments, such as increase in pulmonary vascular resistance because of long-standing high pulmonary artery pressure and flow (ie, Eisenmenger syndrome). In this latter case, the CHF remits at the cost of increasing cyanosis and substantial morbidity and mortality.

CASE RESOLUTION

The case study is typical of an otherwise normal infant with a large VSD who becomes symptomatic with the development of CHF. The baby's growth failure can be attributed to the chronicity of his illness.

The loud murmur and presentation in infancy are strongly suggestive of underlying structural CHD as the cause of CHF. The time of onset of CHF is also suggestive of a specific mechanism. Onset that is slightly delayed after birth is suggestive of a lesion with changing postnatal hemodynamics, such as left-to-right shunt, that has increased as pulmonary resistance has fallen. (A ductus-dependent defect would have presented more acutely and severely in the first week after birth.)

This infant responded fairly well to oral diuretics and digoxin but continued to grow slowly and tire easily, and the VSD showed no signs of spontaneous reduction in size. He underwent surgical repair of the VSD at 5 months of age with an excellent result and no longer has symptoms or requires medication. His growth parameters are now within normal limits, and his prognosis is excellent.

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CHAPTER 105

Chest Pain

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CASE STUDY

A previously healthy 13-year-old boy comes to the office with a report of recurrent chest pain, occurring approximately once a week over the past 2 months. The pain is stabbing in nature, is located at the mid-sternum, is not associated with any other symptoms, and occurs randomly, both at rest and with exercise. It lasts for 2 to 3 minutes, is ranked by the patient as 4 on a severity scale of 10, and subsides spontaneously. He does not appear very concerned about the pain, but his mother is quite anxious to have it checked out. His teacher has sent him home from school twice because of the pain, and the soccer coach will not let him play until he is cleared by a doctor. His physical examination is unremarkable.

Questions

1. What is the significance of chest pain in an otherwise healthy child?
2. How likely is serious heart disease to be heralded by chest pain?
3. How much testing, and what type, is appropriate in the workup for chest pain?
4. Which patients with chest pain should be referred to a cardiologist? To other specialists?

Chest pain in children is among the most common reasons for referral to a pediatric cardiologist, second only to heart murmurs. It is, however, 1 of the least common presenting symptoms of cardiac disease. In fact, from an etiologic standpoint, it would be more suitable to include this chapter in the section on gastrointestinal disorders, respiratory problems, psychological and psychogenic disorders, or hematology, rather than cardiology (Figure 105.1).

Perhaps the strongest reason for addressing chest pain in the cardiology section, along with discussions of heart murmurs, cyanosis, and congestive heart failure, is that it is the greatest fear of the patient, parent or caregiver, and physician that chest pain could herald a serious—even lethal—heart problem in an otherwise healthy pediatric patient. This fear is exacerbated by 2 social phenomena in the United States: the widespread press given to cases of sudden unexpected death in young, apparently healthy athletes (who had not, in fact, experienced chest pain in most cases), and the appropriately high level of concern for the underdiagnosis of ischemic heart disease in the adult population. Public information targeting the adult with chest pain may, unfortunately, be misinterpreted as applying to the child as well. It is this apprehension, and the associated medicolegal defensive posture, that so often drives the patient and the referring primary care physician to seek cardiology consultation and testing. The frequency of such referrals has increased 4- to 5-fold in the past 2 decades, resulting in increasingly inefficient resource utilization.

Epidemiology

The epidemiology of pediatric chest pain is not well studied. Published retrospective studies have attributed chest pain to cardiac causes in 0.25% of patients treated in emergency departments (EDs), 0.3% treated in an outpatient clinic, and 1% treated in a pediatric cardiology clinic.

In the primary care office setting, chest pain is the third most frequent pain symptom, after abdominal pain and headache, accounting for more than 600,000 office visits a year in the United States. The most common age range is 8 to 18 years, peaking between 11 and 13 years of age. No sex or ethnic predilection exists, although the etiologic distribution may vary by sex.

Cardiac causes of chest pain are quite uncommon for 2 reasons. Such pain is either a rare symptom in a common cardiac disorder (eg, aortic stenosis) or caused by a rare condition (eg, anomalous origin of coronary artery [AOCA]).

Clinical Presentation

Substantial variability exists in the symptom of chest pain in children (Box 105.1). Some pediatric patients experience a single, protracted, severe episode that results in a visit to the ED. In that setting, the patient may have other signs or symptoms of an acute medical problem, such as fever, shortness of breath, or hypotension, raising the level of suspicion for a serious organic cause.

More frequently, children report repeated episodes occurring sporadically over a period of months or even years. The pain may be induced or exacerbated by exercise, deep breathing, lying down, or eating. It can begin and end abruptly or gradually. It may be accompanied by other symptoms, which may help in making a diagnosis. In cases in which the pain occurs with exercise, the physician must determine whether it is a consistent, predictable experience, or is unpredictable, as well as whether it is associated with dizziness or syncope.

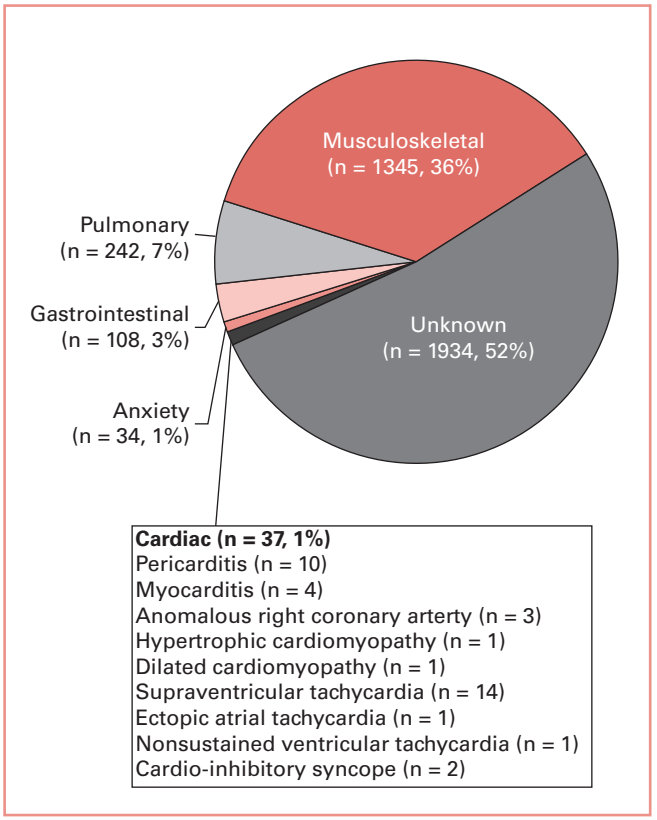

Figure 105.1. Causes of chest pain in a series of 3,700 pediatric patients seen for this symptom during a 10-year period.
Reprinted with permission from Saleeb SF, Li WYV, Warren SZ, Lock JE. Effectiveness of screening for life-threatening chest pain in children. *Pediatrics*. 2011;128(5):e1062–e1068.

Box 105.1. What to Ask

Chest Pain

- What is the pain like? Where is it located? Does it radiate? How severe is it?
- How long has the child been having pain? Did it begin after trauma? How often does the pain occur? How long does it last? Does it start and end suddenly?
- What brings on the pain? Is it related to exercise and, if so, is it consistent?
- Does the child have associated symptoms with the pain, such as syncope, shortness of breath, palpitations, fever, nausea, sour taste, wheezing, or cough?
- Does the child at other times have cardiac symptoms, such as easy fatigability, cyanosis, exertional dyspnea, edema, or syncope?
- Does the child's medical history include potentially pertinent disorders, such as asthma, gastroesophageal reflux disease, psychiatric problems, heart disease, or sickle cell disease?
- How much of an effect is the pain having on the child's life? Is the child missing school or sports?
- Is there a family history of sudden unexpected death, recurrent syncope, or known genetic syndrome?

Up to 97% of children evaluated for chest pain have no serious medical history, and most have an unremarkable physical examination.

Pathophysiology

The pathophysiology varies based on the underlying cause of the pain, and the differential diagnosis is diverse (Box 105.2). It is important for the patient, parent or caregiver, and physician to understand that thoracic or abdominal pain, and visceral pain in particular, is poorly localized. This makes it difficult to distinguish between esophagitis and cardiac ischemia, for example; hence, the term "heartburn" for the former condition. Precordial pain may

Box 105.2. Differential Diagnosis of Chest Pain in Children and Adolescents

Chest Wall

- Trauma[a]
- Overuse[a]
- Inadequate breast support[a]
- Chronic cough[a]
- Costochondritis (Tietze syndrome)[b]
- Precordial catch syndrome[b]
- Slipping rib syndrome[c]

Gastrointestinal

- Gastroesophageal reflux disease[a]
- Esophagitis resulting from repeated vomiting[b]
- Esophageal stricture[c]
- Foreign body[c]

Pulmonary

- Exercise-induced asthma[a]
- Pneumonia[a]
- Pleurodynia, pleurisy[b]
- Pneumothorax/pneumomediastinum[c]
- Pulmonary embolism[c]

Psychological

- Anxiety disorder[a]
- Depression[a]
- Conversion reaction[b]
- Munchausen syndrome[c]
- Bulimia nervosa[c]

Miscellaneous

- Idiopathic[a]
- Acute chest syndrome (in the patient with sickle cell disease)[b]
- Thoracic tumor[c]
- Herpes zoster[c]

Cardiac

- See Box 105.3

[a] Common cause of chest pain.
[b] Uncommon cause of chest pain.
[c] Rare cause of chest pain.

originate from any intrathoracic organ or from the chest wall itself, and the patient cannot identify the source of the discomfort, which in itself is a cause of distress.

Cardiac causes are a heterogeneous category that are best characterized as ischemic or nonischemic in origin (Box 105.3). None of these causes is common. Ischemic chest pain, or angina, is caused by a drop (often sudden) in the myocardial oxygen supply/demand ratio, causing pain or, in rare cases, sudden death. This may occur because of diseased coronary arteries as in adults, resulting from accelerated coronary atherosclerosis, but such an occurrence is quite rare in the pediatric population. Angina may occur in the patient with progeria, mucopolysaccharidosis, post-transplantation coronary disease, or severe familial hypercholesterolemia. Alternatively, it may occur as a result of previous inflammation (as with coronary aneurysm in Kawasaki disease), resulting in coronary artery stenosis. A congenital AOCA from the opposite sinus of Valsalva (Figure 105.2) or from the pulmonary artery may result in ischemia resulting from compression of the anomalous vessel between the great arteries, obstruction from a slit-like orifice at the origin, or, in the case of the pulmonary artery, low pressure and low saturation in the perfusing blood.

The chest pain that occurs in a small minority of patients with severe left ventricular outflow obstruction (ie, aortic valve stenosis and hypertrophic obstructive cardiomyopathy) likely is also the result of ischemia. The already diminished supply/demand ratio resulting from hypertrophy and hypertension of the left ventricle falls further with strenuous exercise, causing pain and/or arrhythmia.

With use of drugs, such as cocaine, chest pain may be attributable to arrhythmia, myocardial hypoperfusion, or a combination of these. This may present as chest pain or overt collapse, in some cases with cardiac arrest.

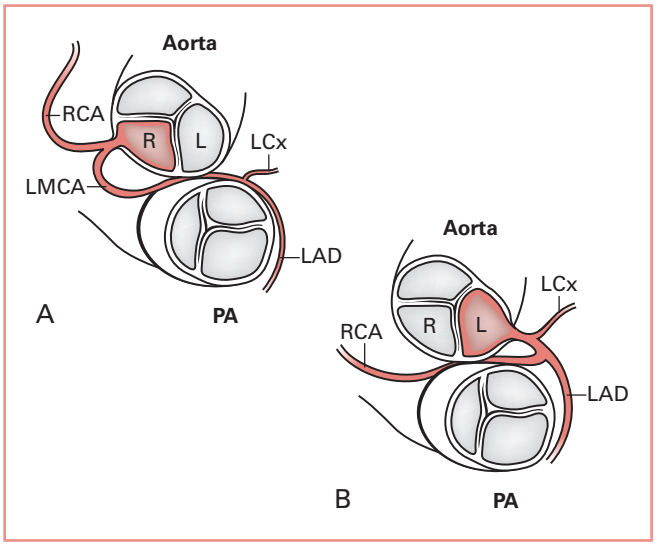

Figure 105.2. Schematic diagram of the 2 forms of anomalous origin of coronary artery from the wrong sinus that are associated with myocardial ischemia. A, Anomalous origin of the left main coronary artery (LMCA) from the right sinus of Valsalva. B, Anomalous origin of the right coronary artery (RCA) from the left sinus of Valsalva. In each case, the anomalous coronary artery can be seen coursing between the aorta and pulmonary artery (PA).

Abbreviations: L, left aortic sinus; LAD, left anterior descending; LCx, left circumflex; R, right aortic sinus.

Box 105.3. Cardiac Causes of Chest Pain in Children

Ischemic

- Tachyarrhythmia (eg, supraventricular tachycardia, ventricular tachycardia)[a]
- Cocaine abuse[a]
- Aortic stenosis[b]
- Hypertrophic obstructive cardiomyopathy[b]
- Anomalous origin of coronary artery[b]
- Accelerated coronary atherosclerosis, such as in progeria, hyperlipidemia, and cardiac transplantation[b]
- Coronary artery stenosis secondary to Kawasaki disease[b]

Nonischemic

- Pericarditis (eg, viral, bacterial, autoimmune, postoperative)[a]
- Mitral valve prolapse[a]
- Myocarditis[b]
- Aortic root dissection, such as in Marfan syndrome[b]

[a] Uncommon cause of chest pain.

[b] Rare cause of chest pain.

Although many children with cardiac arrhythmias are asymptomatic or present with palpitations, dizzy spells, or syncope, some do report chest pain. In the case of the younger child, this may reflect an inability to express the discomfort of palpitations as other than "hurting." Additionally, transient ischemia occurs in some individuals with tachyarrhythmia, such as paroxysmal supraventricular tachycardia (SVT), because of high myocardial oxygen consumption and shortened diastole, which compromises perfusion. In these patients, ST segment depression may be seen on electrocardiography (ECG) during the arrhythmia and may persist for several minutes after the arrhythmia is terminated.

Nonischemic cardiac causes of chest pain include pericarditis and, less commonly, myocarditis, aortic dissection, and mitral valve prolapse. The most common form of inflammatory heart disease is acute viral infection; acute bacterial pericarditis is more severe and associated with greater systemic toxicity. Connective tissue disease, such as lupus erythematosus and juvenile rheumatoid arthritis, is frequently associated with immune-mediated pericarditis, as is the postpericardiotomy syndrome that occurs shortly after cardiac surgery. In these disorders the pain is the result of inflammation of the pericardium and epicardium, which directly stimulates the many sensory nerve endings in this area.

Aortic dissection also results in direct stimulation of pain fibers, in this case in the aortic wall. It is rare in the normal pediatric population but may occur in the setting of Marfan syndrome and

related disorders. Chest pain also occurs in patients with mitral valve prolapse, but it is often difficult to establish a clear causal relationship in this setting. A large percentage of patients with chest pain have a diagnosis of gastroesophageal reflux disease (GERD).

Differential Diagnosis

The differential diagnosis of pediatric chest pain is presented in Box 105.2, with cardiac causes listed in Box 105.3. The relative frequencies of these causes vary in reported series (Figure 105.1); however, all studies report higher frequencies of respiratory, idiopathic, traumatic, and psychogenic etiologies and low frequencies of cardiac etiologies (typical range, 1%–5%) in patients with no previous cardiac history. These data must be viewed as approximations because the ultimate etiologic classification of cases in these series usually is not based on a definitive result but rather an attribution by the physician involved. Therefore, cultural factors and individual preferences may result in higher reported rates of "idiopathic" chest pain in some centers, "chest wall pain" in others, and "anxiety disorder" in yet others. Chest wall pain may be the result of trauma or inflammation of the costochondral cartilages (ie, Tietze syndrome). Some studies report a higher incidence of cardiac etiologies because they so classify any patient with chest pain with a cardiac finding (eg, premature beats, abnormal ECG), regardless of whether it may explain the pain. Among children referred to a cardiologist for evaluation of chest pain, nearly 50% have a psychiatric diagnosis of at least moderate severity; in 29% of referred children, the psychiatric disorder is of marked severity. Anxiety disorders predominate in this subpopulation, but depression also is seen more commonly than in the general population. These children may be referred to a mental health specialist. Other specialists who may become involved in the care of patients with symptoms of chest pains include gastroenterologists (eg, for gastroesophageal reflux) or pulmonologists for lung conditions (eg, for asthma).

Evaluation

Evaluation of the child with chest pain must include a thorough, methodical history and careful physical examination. In many cases such evaluation is sufficient for diagnosis and the formulation of a management plan. "Red flags" that are suggestive of a cardiac cause are listed in Box 105.4.

History

The major questions to be addressed are outlined in Box 105.1. Because many pertinent details must be included in the history of present illness and because these details often are provided in a variable sequence, some physicians find it helpful to use a printed format as a guide. Some offer a questionnaire for the patient or parent/caregiver to complete. Witnesses to the episodes may provide additional helpful information, especially if the patient is not verbally expressive. A witness may estimate a pain score based on observation, which may differ substantially from the patient's self-assigned score.

Pain that occurs repeatedly over time is less likely attributable to an organic cause of a serious nature, particularly if it is not reproducible. A severe, protracted episode (eg, lasting hours) is more likely to be organic in origin. The location of the pain has not been a strong predictor of diagnosis in published series. The timing and association of pain with other symptoms, however, may provide major clues. Reflux esophagitis may occur after eating, more often when a patient is supine or very active, and may be accompanied by a sour taste; it may be relieved by eating or use of an antacid. Associated symptoms that may raise a red flag for a cardiac cause include syncope, palpitations, sweating, and nausea; reproducible pain at a particular level of exertion also has in increased likelihood for being anginal. Because pain and accompanying anxiety may cause sinus tachycardia, which can be interpreted by the patient as palpitations, it is important for the physician to get a sense of the heart rate experienced by patients with that symptom. Children can be asked to tap their chest or clap their hands as fast as the heart was racing during the palpitations; serious tachyarrhythmias, such as SVT and ventricular tachycardia, are usually quite rapid.

Box 105.4. Red Flag Items That Warrant Cardiology Referral for Pediatric Chest Pain

Patient History
- Chest pain with exertion
- Exertional syncope
- Chest pain that radiates to the back, jaw, left arm, or left shoulder
- Chest pain that increases with supine position
- Chest pain that is temporally associated with fever >38.4°C (>101.1°F)

Past Medical History
- Hypercoagulable state
- Arthritis/vasculitis
- Immobilization

Family History
- Sudden unexplained death
- Cardiomyopathy
- Hypercoagulable state

Physical Examination
- Respiratory rate >40 breaths per minute
- Temperature >38.4°C (>101.1°F)
- Ill-appearing
- Painful/swollen extremities
- Non-innocent murmur (see Chapter 101)
- Distant heart sounds
- Gallop
- Loud pulmonic component of S2
- Pericardial friction rub
- Peripheral edema

The presence of other symptoms may suggest etiology of the chest pain. For example, fever and malaise are common in the setting of pneumonia, pleurisy, or pericarditis. In exercise-induced asthma (EIA), chest pain may be related to exertion and is also accompanied by cough and/or wheezing. Shortness of breath, which may be related to pulmonary pathology, may also reflect anxiety or pain with movement.

In pediatric patients with psychogenic pain, other symptoms of anxiety or depression may be reported, although not necessarily simultaneously with the chest pain and often preceding it in onset. A history of recent stressors may be elicited. These patients may also report other recurrent somatic symptoms.

The nature, severity, and abruptness of the pain may also yield diagnostic clues. Exercise-induced asthma is often described as a chest "tightness," usually is gradual in onset, and lasts beyond the exertion itself. *Precordial catch syndrome*, a poorly understood disorder also known as *Texidor twinge,* is a sudden sharp, localized pain that is exacerbated by deep breathing and lasts only seconds or minutes. In contrast, *slipping rib syndrome*, in which the cartilaginous tips of ribs 8, 9, and 10 become transiently subluxated, produces pain at the costal margin, is quite sensitive to movement, and is often associated with a "popping" or "slipping" sensation in the affected area. The pain of GERD usually is described as "burning" and may awaken the patient from sleep. In contrast, the pain of angina is reported as "crushing" and may radiate to the left arm or the neck. The diffuse pain of pericarditis often is ameliorated by sitting forward. Aortic dissection, a rare cause of chest pain in children, results in an acute, tearing sensation and usually is diagnosed in the ED.

A history of recent chest trauma is suggestive of chest wall injury as the cause of pain; however, the fall or sports mishap may be forgotten if the onset of the pain is not temporally associated with the event. Chest wall pain also may result from overuse, as in weight lifters, or from inadequate breast support, as in female runners. Substance use, particularly with cocaine, may be disclosed if the patient is questioned in private. In some cases cocaine use may have occurred several days before the onset of pain.

A positive medical history may help the physician identify the underlying diagnosis. In the child with sickle cell disease, acute chest syndrome must be considered early in the assessment. A history of respiratory disease may point to either an acute respiratory infection or EIA. Depending on the cardiac diagnosis, the child with known heart disease who may experience benign chest pain is more likely to have a cardiac etiology than otherwise healthy peers. Most congenital heart defects, for example, do not cause pain but may raise the level of anxiety in the family and result in the perception or exaggeration of chest pain. Of greater concern is a history of heart disease that may affect myocardial perfusion, such as Kawasaki disease affecting the coronary arteries, or cardiac surgery involving the coronary arteries (eg, arterial switch operation for transposition of the great arteries).

The family history must not be overlooked. Although in most cases pediatric chest pain is not the result of a hereditary disorder, some of the more severe causes may be hereditary, such as hypertrophic cardiomyopathy, some arrhythmias, asthma, sickle cell disease, and aortic dissection in Marfan syndrome. It also has been noted that the child with nonorganic chest pain (eg, psychogenic pain) may have a close relative who has undergone recent heart surgery or a had heart attack, bringing attention to the heart during a time of emotional stress.

A complete review of systems is essential in the assessment of the child with chest pain because of the wide range of differential diagnoses.

Physical Examination

A careful physical examination is imperative. In the child with no history of serious illness, the examination should be focused on, but not limited to, the chest. General inspection will immediately aid in distinguishing between the acutely ill child and the otherwise well child with chest pain. Abnormal vital signs, such as fever, tachycardia, or tachypnea, are associated with acute etiologies, such as infection or inflammation. The child's pain level should be quantified with the aid of a pain scale. If the patient is dyspneic, pulse oximetry should be measured.

The chest wall should be examined for signs of trauma and for tenderness. Care must be taken with the latter because it is easy to elicit a false-positive examination for costochondritis, for example, because the costochondral junctions have some degree of normal tenderness, as do the breasts of female patients. Asymmetry of tenderness and a report that the pain produced is similar to that experienced is suggestive of chest wall injury. In the patient with rib injury, the pain can be elicited not only on direct palpation but also indirectly by compression of the thoracic cage from another location. In a girl with inadequate breast support, the breast ligaments may be symmetrically tender.

Auscultation of the lungs and heart yields useful clues to diagnosis, especially in the child with an acute inflammatory process (eg, rales, rub) and in the child with left ventricular outflow obstruction, such as aortic stenosis (eg, murmur). It is important to remember, however, that many organic causes of chest pain, such as GERD, EIA, intermittent arrhythmias, and AOCA, are undetectable on physical examination if the patient is not experiencing the pain at the time of the visit.

Other aspects of the physical examination may also aid in the evaluation of the child with chest pain. Jugular distention, hepatomegaly, and peripheral edema are suggestive of congestive heart failure or pericardial effusion with tamponade. The child's behavior pattern and interaction with parent or caregiver may be suggestive of a psychological disorder, such as anxiety or depression. Poor dentition and halitosis in an adolescent with weight loss may be a sign of bulimia as a source of esophagitis. Excessive signs of trauma, such as multiple ecchymoses, may be indicative of coagulopathy and also raise the possibility of nonaccidental trauma. Marfanoid habitus is suggestive of a connective tissue disorder with secondary aortic involvement.

Laboratory and Imaging Studies

A variety of diagnostic studies is available. It is incumbent on the physician to select studies appropriate to the individual patient, guided by the history and physical examination findings.

In the patient presenting with acute chest pain (often to the ED), the need for tests is increased because the differential diagnosis more often includes serious, even life-threatening, disorders compared with that of the child with chronic recurrent pain. Per published series, chest radiography has a reasonably high yield of positive findings. A negative radiographic finding is reassuring in ruling out pathology such as pleural effusion, pneumonia, pneumothorax, pneumomediastinum, and thoracic tumor; however, it cannot be used to exclude most cardiac etiologies. More detailed imaging, such as magnetic resonance imaging, may be necessary when major chest trauma is reported or aortic dissection is suspected. Dyspnea or hypoxemia, particularly in the setting of recent immobilization or in an adolescent female taking oral contraceptives, is suspicious for pulmonary embolism, for which a spiral computed tomography or nuclear perfusion scan is indicated. A D-dimer assay may be positive but is not highly sensitive for pulmonary embolism in children.

Although ECG is routinely performed as part of the evaluation for acute chest pain in children, it is rarely helpful in establishing a diagnosis other than arrhythmia, which may be suspected from the history or physical examination. Changes in ST segment may reflect pericardial irritation or myocardial ischemia if the ECG is performed at the time of the pain. If ongoing myocardial ischemia is suspected, myocardial enzymes (ie, creatine kinase-MB [CK-MB] fraction, troponin I) should be measured and toxicology screening performed. If signs of acute infection (eg, fever) are noted, a complete blood cell count, erythrocyte sedimentation rate or C-reactive protein level, and appropriate cultures are indicated. Echocardiography is highly sensitive and specific for pericardial effusion and should be performed early in the evaluation of the patient with chest pain and jugular distention, a friction rub, fever, or ST segment elevation on ECG.

In the patient who presents with chronic recurrent chest pain, the likelihood of serious pathology is quite low. In the setting of a normal physical examination a reassuring history, the yield of "screening" tests such as chest radiography and ECG is extremely poor, and the cost in dollars and anxiety is not justifiable. In most cases the history and physical examination are adequate to identify a focused selection of diagnostic tests, if any are necessary. For example, in the patient who describes pain suggestive of esophagitis endoscopy or an upper gastrointestinal series may be appropriate. When EIA is suspected, pulmonary function testing is appropriate, in some cases with an exercise challenge. Strong suspicion for psychogenic causes should prompt further psychological evaluation at the initial encounter, including querying the patient about suicidal ideation; further testing or consultation may be indicated.

The finding of a murmur of left ventricular outflow tract obstruction is an indication for echocardiography to confirm the diagnosis and yield further details to guide management. A history of palpitations or syncope may be suggestive of arrhythmia. Electrocardiography may be diagnostic for Wolff-Parkinson-White syndrome as a substrate for SVT; however, normal ECG does not rule out arrhythmia if the patient is asymptomatic at the time of the study. In such a patient, an ambulatory ECG, such as a Holter or patch monitor or a transtelephonic event detector may enable documentation of the rhythm during an episode of pain. Consistent exertional pain merits evaluation for ischemia, with resting ECG and often exercise stress testing. However, it is important to note that these studies can be negative between episodes in patients with AOCA. A diagnosis of AOCA can be identified on echocardiography, but only if the study is deliberately directed toward that diagnosis; therefore, the study should be done in a pediatric echocardiography laboratory, and the sonographer must be aware of the diagnosis in question. Further delineation of this anatomy usually requires computed tomography angiography.

Management

The management of pediatric chest pain depends on the underlying diagnosis or lack thereof. Strong suspicion of cardiac pathology, either on the basis of history and physical examination or on the basis of subsequent testing as described previously, warrants prompt referral to a pediatric cardiologist. Management may include surgery (eg, for AOCA), antibiotics, nonsteroidal anti-inflammatory drugs, pericardiocentesis (eg, for pericarditis), antiarrhythmics, interventional catheterization (eg, balloon angioplasty, radiofrequency ablation), or some combination of these treatments.

Short-term nonsteroidal anti-inflammatory drugs are helpful for chest wall pain resulting from overuse, trauma, costochondritis, or slipping rib syndrome. In a minority of cases, local injection with an anesthetic may be necessary.

In some cases, therapeutic trials may be considered to arrive at a diagnosis. A child with suspected esophagitis may be given an antacid at the time of the pain. If the pain is relieved, further workup and treatment can proceed accordingly. Similarly, a pediatric patient with suspected EIA, particularly one with a previous history of reactive airways disease, may benefit from a trial of an inhaled bronchodilator at the time of the pain.

In the exceedingly common setting of benign chest pain, such as with minor chest wall trauma, mild somatization, or occasional reflux esophagitis, the most important step in management is reassurance of the patient and family that this is not an indication of a serious disorder. It is essential for the physician to clarify how this conclusion has been reached and why further testing is not appropriate.

A frequent observation in this setting is that most families do not require a definitive diagnosis of the cause of the pain. If a serious disorder is excluded, which is necessary because 50% of patients believe that chest pain indicates heart disease, all parties are reassured. Follow-up studies have demonstrated that at least 80% of patients in this category do not seek further medical attention for their chest pain, nor do they return for follow-up.

Prognosis

The outcome depends on the underlying diagnosis. Most cases of benign chest pain resolve spontaneously, often within a short time after evaluation. Psychogenic chest pain has a greater tendency for recurrence than other forms. Even with serious and potentially life-threatening causes of chest pain, early diagnosis and intervention usually results in an excellent outcome.

CASE RESOLUTION

The patient and his parents are assured that he has no evidence of a serious medical or psychiatric problem. His heart is strong, his lungs clear, and his circulation good. The patient and family are reassured that chest pain in otherwise healthy children may be mysterious but is common and rarely is a sign of illness. They are gently but definitively advised that the patient requires no further evaluation at this time, but that if the problem does not resolve itself, the child should return for reevaluation.

The boy is delighted to hear that he may return to full sports participation, which is confirmed in writing to the coach. The parents are relieved and grateful for the attention and reassurance of the physician. At subsequent office visits for other purposes, the patient reports no more episodes of chest pain.

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CHAPTER 106

Hypertension

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CASE STUDY

A 16-year-old girl is seen in the emergency department with a history of persistent headaches of 2 weeks' duration. She has been having occasional headaches for the past 2 years, which have been treated primarily with acetaminophen. She denies any recent weight loss, hair loss, joint pain, sweating, or palpitations. She has no history of swelling of her eyes or legs or blood noticed in the urine. She was born preterm at 30 weeks' gestational age and was kept in the hospital for 2 weeks. She has no history of urinary tract infection. Her 34-year-old mother and 58-year-old maternal grandmother have been on antihypertensive agents for the past several years; however, she has no family history of renal or heart disease. She is an average student. Her diet includes mostly meat and refined carbohydrates, such as bread and pasta. Additionally, she regularly eats salty snacks but drinks soda only occasionally. She has never been involved in any physical activity on a regular basis. She has never been sexually active and denies the use of illicit drugs, alcohol, or tobacco. She denies taking any medication prior to this visit, including oral contraceptives.

The physical examination is remarkable for a girl with weight, height, and body mass index above the 95th percentile for age. Her pulse is 85 beats per minute, and her blood pressure is 158/78 mm Hg in the right arm in the supine position. Equal pulses are palpable in all 4 extremities. Blood pressure is 164/92 mm Hg in the right lower extremity. Funduscopic examination reveals evidence of arteriovenous nicking but no papilledema. Normal breath sounds are noted on chest examination, along with an active precordium with the apical impulse shifted to the left. No murmurs are heard. The liver is palpable 1 cm below the right costal margin. The neurologic examination is unremarkable; no focal neurologic deficit is present. Urinalysis is normal. Hemoglobin is 11.2 g/dL, and hematocrit is 33%. Sodium is 139 mEq/L, potassium is 3.8 mEq/L, chloride is 102 mEq/L, and bicarbonate is 22 mEq/L. Blood urea nitrogen is 15 mg/dL, and serum creatinine is 0.9 mg/dL. Electrocardiography shows left ventricular enlargement. Computed tomography of the head is normal.

Questions

1. What is the definition of hypertension in children and adolescents?
2. What are the causes of hypertension in children and adolescents?
3. What is the appropriate evaluation of hypertension in children and adolescents?
4. What are the comorbid conditions and long-term complications associated with essential (ie, primary) hypertension?
5. What is the appropriate emergency treatment of symptomatic hypertension?
6. What is the long-term management of children and adolescents with essential hypertension?

Hypertension (HTN) has become a highly concerning chronic noncommunicable medical condition among children and adolescents in the past few decades because of a multitude of factors including, but not limited to, increasing prevalence of childhood obesity, survival of children with renal anomalies, and children born preterm who often sustain hypoxic injuries to the kidneys. *Hypertension* is blood pressure (BP) that is elevated above the normative BP data based on age, sex, and height.

Hypertension takes primary and secondary forms. Primary HTN is the most predominant cause among pediatric patients in the United States. General characteristics of patients with primary HTN include age of 13 years or older, family history of HTN, and overweight or obesity. Primary HTN in pediatrics has become a major public health concern. Secondary HTN is proportionally more prevalent among younger children and has an underlying cause that, if identified, may be curable, thereby eliminating the need for lifelong medical treatment. Renal and renovascular disease are the most common causes of secondary HTN. With early diagnosis and intervention, however, the long-term adverse consequences of HTN can be prevented. Children who are expected to be at increased risk for end-organ (ie, heart, central nervous system, kidneys, eyes) damage are those with persistently elevated BP, high body mass index (BMI), excessive weight gain, comorbid conditions (eg, type 2 diabetes), and a family history of HTN.

Normal Blood Pressure and Definition of Hypertension

Systolic and diastolic BP gradually increase from the newborn period through adolescence; therefore, age-appropriate norms should be used to classify a BP reading as normal or hypertensive. The stages and age-appropriate values of HTN are defined by the American

Academy of Pediatrics (AAP) "Clinical Practice Guideline (CPG) for Screening and Management of High Blood Pressure in Children and Adolescents," published in August 2017. The newer version of the previous BP chart published by AAP CPG compared with the previous guidelines *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* excluded children with obesity in the analysis and included height values rather than height percentiles for easier reference.

The classification of BP consists of normal BP, elevated BP, stage 1 HTN, and stage 2 HTN. In the most recent AAP CPG, the term "prehypertension" was replaced with "elevated BP." Currently, the stages of HTN are defined differently for children younger than 13 years than for adolescents age 13 years or older (Table 106.1, Table 106.2, and Table 106.3). For neonates and for infants age 1 through 12 months, similar guidelines for diagnosing HTN apply (Table 106.4, Table 106.5A, and Table 106.5B). For a diagnosis of HTN, measurement in any of the ranges provided must be noted on 3 or more occasions.

Definition of White Coat Hypertension and Masked Hypertension

It is well known that BP measurements are dynamic and can be misleading in a single clinic visit. Recent knowledge from ambulatory BP monitoring (ABPM) has contributed substantially to the understanding of HTN in children by revealing different BP responses under different circumstances. Ambulatory BP monitoring is continuous and assesses changes in BP over a 24-hour period, noting changes in BP at various intervals throughout the day and night. Ambulatory BP monitoring has helped identify 2 situations in which the BP measured during the clinical visit may significantly differ from home: white coat HTN and masked HTN (Table 106.6).

Table 106.1. Definition of Hypertension in Children and Adolescents

	Definition	
Term	*<13 years*	*≥13 years*
Normal BP	Systolic and diastolic BP <90th percentile for age, sex, and height	<120/<80 mm Hg
Elevated BP	Average systolic or average diastolic BP of 90th–94th percentiles for age, sex, and height	120/<80 mm Hg to 129/<80 mm Hg
Stage 1 hypertension	Average systolic and/or diastolic BP ≥95th percentile through the 94th percentile + 12 mm Hg for age, sex, and height with measurements obtained on ≥3 occasions	130/80 mm Hg to 139/89 mm Hg
Stage 2 hypertension	Average systolic and/or diastolic BP >5 mm Hg above the 95th percentile for age, sex, and height	≥140/90 mm Hg

Abbreviation: BP, blood pressure.

With *white coat HTN*, isolated elevated BP measurements in the hypertensive range are noted in the clinic, but the patient has otherwise normal values outside the medical setting. White coat HTN can account for a significant number of elevated BP readings in clinics, possibly in up to 50% of patients. These isolated elevated values may result in a misinterpretation of a child's actual BP values.

With *masked HTN*, however, the child or adolescent at risk for HTN has normal BP measurements in the office but has hypertensive BP measurements outside the office. The child with masked HTN is twice as likely as a child who is not hypertensive to have a family history of HTN. If the child also has a high pulse rate and elevated BMI, the child is at increased risk for developing a cardiovascular disorder. It is important to promptly identify and diagnose masked HTN because left untreated, it can put the patient at significant risk for end-organ damage, resulting in stroke, left ventricular hypertrophy (LVH), visual impairment, and/or renal failure. Studies have shown a significant direct association between not only elevated BP and left ventricular mass index but also between white coat and masked HTN and left ventricular mass index. The prevalence and long-term implications of the latter 2 types of HTN remain unclear.

Accurate Method of Measuring Blood Pressure

It is essential to obtain an accurate BP measurement in children. Several factors can influence BP measurement, and proper planning is important to optimize the likelihood of obtaining an accurate measurement. Prior to measurement, the child should be seated for 3 to 5 minutes with the back supported and with the feet uncrossed and resting on a firm surface to ensure an accurate reading. An appropriately sized BP cuff should be used based on the child's arm circumference and length; the inner cuff width should be approximately 40% of the arm circumference midway between the olecranon and the acromion, and the length should be greater than 80% around the arm circumference at the same point to avoid an inaccurately high reading (Figure 106.1). The right arm should be used for consistency in comparison with standard tables. In addition to using a variety of cuff sizes, it is recommended to use a thigh cuff in children and adolescents whose BMI is greater than the 95th percentile and in cases in which all standard arm cuffs are too small. For the child with suspected coarctation of aorta, the child should be in a prone position, lying on a flat surface, and the thigh cuff should be placed at the mid-thigh level. Of note, the BP in the lower extremities is usually 10% to 20% higher than the brachial artery pressures (Table 106.7).

Various other factors to consider to minimize errors while measuring BP include the patient's posture (ie, sitting versus lying down) and level of the arm in relation to level of the heart (ie, the elbow should be at the level of the heart). It is also important that the child remain calm and not be anxious or agitated while the measurement is taken. Additionally, the person taking the measurement must ensure that the child has not ingested any stimulants (eg, caffeinated beverages, dietary supplements) that could artificially increase BP measurement within 30 to 60 minutes before testing.

Text continued on page 793

Table 106.2. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Boys Ages 1 Through 13 Years by Percentiles of Height

		SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
Age (y)	BP Percentile	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	30.4	30.8	31.6	32.4	33.3	34.1	34.6	30.4	30.8	31.6	32.4	33.3	34.1	34.6
	Height (cm)	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
	50th	85	85	86	86	87	88	88	40	40	40	41	41	42	42
	90th	98	99	99	100	100	101	101	52	52	53	53	54	54	54
	95th	102	102	103	103	104	105	105	54	54	55	55	56	57	57
	95th + 12 mm Hg	114	114	115	115	116	117	117	66	66	67	67	68	69	69
2	Height (in)	33.9	34.4	35.3	36.3	37.3	38.2	38.8	33.9	34.4	35.3	36.3	37.3	38.2	38.8
	Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	50th	87	87	88	89	89	90	91	43	43	44	44	45	46	46
	90th	100	100	101	102	103	103	104	55	55	56	56	57	58	58
	95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	95th + 12 mm Hg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height (in)	36.4	37	37.9	39	40.1	41.1	41.7	36.4	37	37.9	39	40.1	41.1	41.7
	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	50th	88	89	89	90	91	92	92	45	46	46	47	48	49	49
	90th	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th + 12 mm Hg	118	118	119	119	120	121	121	72	73	73	74	75	76	76
4	Height (in)	38.8	39.4	40.5	41.7	42.9	43.9	44.5	38.8	39.4	40.5	41.7	42.9	43.9	44.5
	Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	50th	90	90	91	92	93	94	94	48	49	49	50	51	52	52
	90th	102	103	104	105	105	106	107	60	61	62	62	63	64	64
	95th	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	95th + 12 mm Hg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height (in)	41.1	41.8	43.0	44.3	45.5	46.7	47.4	41.1	41.8	43.0	44.3	45.5	46.7	47.4
	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	50th	91	92	93	94	95	96	96	51	51	52	53	54	55	55
	90th	103	104	105	106	107	108	108	63	64	65	65	66	67	67

(*Continued*)

Table 106.2. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Boys Ages 1 Through 13 Years by Percentiles of Height (*continued*)

		SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
Age (y)	BP Percentile	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height (in)	43.4	44.2	45.4	46.8	48.2	49.4	50.2	43.4	44.2	45.4	46.8	48.2	49.4	50.2
	Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	50th	93	93	94	95	96	97	98	54	54	55	56	57	57	58
	90th	105	105	106	107	109	110	110	66	66	67	68	68	69	69
	95th	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	95th + 12 mm Hg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height (in)	45.7	46.5	47.8	49.3	50.8	52.1	52.9	45.7	46.5	47.8	49.3	50.8	52.1	52.9
	Height (cm)	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	50th	94	94	95	97	98	98	99	56	56	57	58	58	59	59
	90th	106	107	108	109	110	111	111	68	68	69	70	70	71	71
	95th	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	95th + 12 mm Hg	122	122	123	124	126	127	128	83	83	84	85	85	86	86
8	Height (in)	47.8	48.6	50	51.6	53.2	54.6	55.5	47.8	48.6	50	51.6	53.2	54.6	55.5
	Height (cm)	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	50th	95	96	97	98	99	99	100	57	57	58	59	59	60	60
	90th	107	108	109	110	111	112	112	69	70	70	71	72	72	73
	95th	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	95th + 12 mm Hg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height (in)	49.6	50.5	52	53.7	55.4	56.9	57.9	49.6	50.5	52	53.7	55.4	56.9	57.9
	Height (cm)	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	50th	96	97	98	99	100	101	101	57	58	59	60	61	62	62
	90th	107	108	109	110	112	113	114	70	71	72	73	74	74	74
	95th	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	95th + 12 mm Hg	124	124	125	127	128	130	131	86	86	87	88	88	89	89

Table 106.2. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Boys Ages 1 Through 13 Years by Percentiles of Height (*continued*)

		SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
Age (y)	BP Percentile	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
10	Height (in)	51.3	52.2	53.8	55.6	57.4	59.1	60.1	51.3	52.2	53.8	55.6	57.4	59.1	60.1
	Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	145.9	150.1	152.7
	50th	97	98	99	100	101	102	103	59	60	61	62	63	63	64
	90th	108	109	111	112	113	115	116	72	73	74	74	75	75	76
	95th	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	95th + 12 mm Hg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height (in)	53	54	55.7	57.6	59.6	61.3	62.4	53	54	55.7	57.6	59.6	61.3	62.4
	Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
	50th	99	99	101	102	103	104	106	61	61	62	63	63	63	63
	90th	110	111	112	114	116	117	118	74	74	75	75	75	76	76
	95th	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	95th + 12 mm Hg	126	126	128	130	132	135	136	89	90	90	90	90	90	90
12	Height (in)	55.2	56.3	58.1	60.1	62.2	64	65.2	55.2	56.3	58.1	60.1	62.2	64	65.2
	Height (cm)	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	50th	101	101	102	104	106	108	109	61	62	62	62	62	63	63
	90th	113	114	115	117	119	121	122	75	75	75	75	75	76	76
	95th	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	95th + 12 mm Hg	128	129	130	133	136	138	140	90	90	90	90	90	91	91
13	Height (in)	57.9	59.1	61	63.1	65.2	67.1	68.3	57.9	59.1	61	63.1	65.2	67.1	68.3
	Height (cm)	147	150	154.9	160.3	165.7	170.5	173.4	147	150	154.9	160.3	165.7	170.5	173.4
	50th	103	104	105	108	110	111	112	61	60	61	62	63	64	65
	90th	115	116	118	121	124	126	126	74	74	74	75	76	77	77
	95th	119	120	122	125	128	130	131	78	78	78	78	80	81	81
	95th + 12 mm Hg	131	132	134	137	140	142	143	90	90	90	90	92	93	93

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Adapted with permission from Flynn JT, Kaelber DC, Baker-Smith CM, et al; American Academy of Pediatrics Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904.

Table 106.3. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Girls Ages 1 Through 13 Years by Percentiles of Height

		SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
Age (y)	BP Percentile	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	29.7	30.2	30.9	31.8	32.7	33.4	33.9	29.7	30.2	30.9	31.8	32.7	33.4	33.9
	Height (cm)	75.4	76.6	78.6	80.8	83	84.9	86.1	75.4	76.6	78.6	80.8	83	84.9	86.1
	50th	84	85	86	86	87	88	88	41	42	42	43	44	45	46
	90th	98	99	99	100	101	102	102	54	55	56	56	57	58	58
	95th	101	102	102	103	104	105	105	59	59	60	60	61	62	62
	95th + 12 mm Hg	113	114	114	115	116	117	117	71	71	72	72	73	74	74
2	Height (in)	33.4	34	34.9	35.9	36.9	37.8	38.4	33.4	34	34.9	35.9	36.9	37.8	38.4
	Height (cm)	84.9	86.3	88.6	91.1	93.7	96	97.4	84.9	86.3	88.6	91.1	93.7	96	97.4
	50th	87	87	88	89	90	91	91	45	46	47	48	49	50	51
	90th	101	101	102	103	104	105	106	58	58	59	60	61	62	62
	95th	104	105	106	106	107	108	109	62	63	63	64	65	66	66
	95th + 12 mm Hg	116	117	118	118	119	120	121	74	75	75	76	77	78	78
3	Height (in)	35.8	36.4	37.3	38.4	39.6	40.6	41.2	35.8	36.4	37.3	38.4	39.6	40.6	41.2
	Height (cm)	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	50th	88	89	89	90	91	92	93	48	48	49	50	51	53	53
	90th	102	103	104	104	105	106	107	60	61	61	62	63	64	65
	95th	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	95th + 12 mm Hg	118	118	119	120	121	122	122	76	77	77	78	79	80	81
4	Height (in)	38.3	38.9	39.9	41.1	42.4	43.5	44.2	38.3	38.9	39.9	41.1	42.4	43.5	44.2
	Height (cm)	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	50th	89	90	91	92	93	94	94	50	51	51	53	54	55	55
	90th	103	104	105	106	107	108	108	62	63	64	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height (in)	40.8	41.5	42.6	43.9	45.2	46.5	47.3	40.8	41.5	42.6	43.9	45.2	46.5	47.3
	Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	50th	90	91	92	93	94	95	96	52	52	53	55	56	57	57

Table 106.3. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Girls Ages 1 Through 13 Years by Percentiles of Height (*continued*)

		SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
Age (y)	BP Percentile	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
	90th	104	105	106	107	108	109	110	64	65	66	67	68	69	70
	95th	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	95th + 12 mm Hg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height (in)	43.3	44	45.2	46.6	48.1	49.4	50.3	43.3	44	45.2	46.6	48.1	49.4	50.3
	Height (cm)	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	50th	92	92	93	94	96	97	97	54	54	55	56	57	58	59
	90th	105	106	107	108	109	110	111	67	67	68	69	70	71	71
	95th	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	95th + 12 mm Hg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height (in)	45.6	46.4	47.7	49.2	50.7	52.1	53	45.6	46.4	47.7	49.2	50.7	52.1	53
	Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	50th	92	93	94	95	97	98	99	55	55	56	57	58	59	60
	90th	106	106	107	109	110	111	112	68	68	69	70	71	72	72
	95th	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	95th + 12 mm Hg	121	122	123	124	125	126	127	84	84	85	85	86	86	87
8	Height (in)	47.6	48.4	49.8	51.4	53	54.5	55.5	47.6	48.4	49.8	51.4	53	54.5	55.5
	Height (cm)	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	50th	93	94	95	97	98	99	100	56	56	57	59	60	61	61
	90th	107	107	108	110	111	112	113	69	70	71	72	72	73	73
	95th	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	95th + 12 mm Hg	122	123	124	125	127	128	129	84	85	86	86	87	87	87
9	Height (in)	49.3	50.2	51.7	53.4	55.1	56.7	57.7	49.3	50.2	51.7	53.4	55.1	56.7	57.7
	Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	50th	95	95	97	98	99	100	101	57	58	59	60	60	61	61
	90th	108	108	109	111	112	113	114	71	71	72	73	73	73	73
	95th	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	95th + 12 mm Hg	124	124	125	126	128	129	130	86	86	87	87	87	87	87

(*Continued*)

Table 106.3. Blood Pressure Levels for the 90th and 95th Percentiles of Blood Pressure for Girls Ages 1 Through 13 Years by Percentiles of Height (*continued*)

Age (y)	BP Percentile	SBP (mm Hg) Height Percentile or Measured Height							DBP (mm Hg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
10	Height (in)	51.1	52	53.7	55.5	57.4	59.1	60.2	51.1	52	53.7	55.5	57.4	59.1	60.2
	Height (cm)	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	50th	96	97	98	99	101	102	103	58	59	59	60	61	61	62
	90th	109	110	111	112	113	115	116	72	73	73	73	73	73	73
	95th	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	95th + 12 mm Hg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height (in)	53.4	54.5	56.2	58.2	60.2	61.9	63	53.4	54.5	56.2	58.2	60.2	61.9	63
	Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	50th	98	99	101	102	104	105	106	60	60	60	61	62	63	64
	90th	111	112	113	114	116	118	120	74	74	74	74	74	75	75
	95th	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	95th + 12 mm Hg	127	128	129	130	132	135	136	88	89	89	89	89	89	89
12	Height (in)	56.2	57.3	59	60.9	62.8	64.5	65.5	56.2	57.3	59	60.9	62.8	64.5	65.5
	Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	50th	102	102	104	105	107	108	108	61	61	61	62	64	65	65
	90th	114	115	116	118	120	122	122	75	75	75	75	76	76	76
	95th	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	95th + 12 mm Hg	130	131	132	134	136	137	138	90	90	90	90	91	91	91
13	Height (in)	58.3	59.3	60.9	62.7	64.5	66.1	67	58.3	59.3	60.9	62.7	64.5	66.1	67
	Height (cm)	148.1	150.6	154.7	159.2	163.7	167.8	170.2	148.1	150.6	154.7	159.2	163.7	167.8	170.2
	50th	104	105	106	107	108	108	109	62	62	63	64	65	65	66
	90th	116	117	119	121	122	123	123	75	75	75	76	76	76	76
	95th	121	122	123	124	126	126	127	79	79	79	79	80	80	81
	95th + 12 mm Hg	133	134	135	136	138	138	139	91	91	91	91	92	92	93

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Adapted with permission from Flynn JT, Kaelber DC, Baker-Smith CM, et al; American Academy of Pediatrics Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.

Table 106.4. Blood Pressure Levels for Neonatal to 44 Weeks Postconceptional Age			
Postconceptional Age	*50th Percentile*	*95th Percentile*	*99th Percentile*
44 Weeks			
SBP	88	105	110
DBP	50	68	73
MAP	**63**	**80**	**85**
42 Weeks			
SBP	85	98	102
DBP	50	65	70
MAP	**62**	**76**	**81**
40 Weeks			
SBP	80	95	100
DBP	50	65	70
MAP	**60**	**75**	**80**
38 Weeks			
SBP	77	92	97
DBP	50	65	70
MAP	**59**	**74**	**79**
36 Weeks			
SBP	72	87	92
DBP	50	65	70
MAP	**57**	**72**	**71**
34 Weeks			
SBP	70	85	90
DBP	40	55	60
MAP	**50**	**65**	**70**
32 Weeks			
SBP	68	83	88
DBP	40	55	60
MAP	**48**	**62**	**69**
30 Weeks			
SBP	65	80	85
DBP	40	55	60
MAP	**48**	**65**	**68**
28 Weeks			
SBP	60	75	80
DBP	38	50	54
MAP	**45**	**58**	**63**
26 Weeks			
SBP	55	72	77
DBP	30	50	56
MAP	**38**	**57**	**63**

Abbreviations: DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

Reprinted with permission from Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. *Pediatr Nephrol.* 2012;27(1):17–32.

Table 106.5A. Blood Pressure Levels for Infants 1 Month Through 12 Months for Boys													
Age in Months	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
SBP	72	84	90	90	90	90	90	90	90	90	90	90	90
50th percentile													
DBP	56	53	50	50	52	53	54	54	55	56	57	57	57
SBP	87	101	106	106	106	106	106	106	106	106	106	106	106
90th percentile													
DBP	68	65	63	63	63	65	66	67	68	68	69	69	69
SBP	91	103	110	110	110	110	110	110	110	110	110	110	110
95th percentile													
DBP	72	68	66	66	66	70	71	72	72	72	73	73	74

Table 106.5B. Blood Pressure Levels for Infants 1 Month Through 12 Months for Girls													
Age in Months	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
SBP	66	83	87	88	90	90	90	90	90	90	90	90	90
50th percentile													
DBP	55	53	52	52	53	53	53	53	54	54	54	54	54
SBP	76	98	101	104	105	106	106	106	106	106	106	105	105
90th percentile													
DBP	68	65	64	64	65	65	66	66	66	67	67	67	67
SBP	91	103	105	106	107	110	110	110	110	110	110	110	110
95th percentile													
DBP	72	68	67	67	68	70	70	72	72	72	72	72	72

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Reprinted with permission from Mistry K, Gupta C. Neonatal hypertension. *NeoReviews*. 2017;18(6)e357–e371.

Table 106.6. Staging of Ambulatory Blood Pressure Monitoring Values in Children			
Stage	*Clinical SBP or DBP*[a]	*Mean Ambulatory SBP or DBP*[a]	*SBP Load*[b]
Normal BP	Age <13 years: <90th percentile Age ≥13 years: <120/<80 mm Hg	Age <13 years: <95th percentile Age ≥13 years: <120/<80 mm Hg	<25%
Elevated BP	Age <13 years: ≥90th percentile to <95th Age ≥13 years: 120/<80 to <129/<80 mm Hg	Age <13 years: ≥90th percentile to <95th percentile Age ≥13 years: 120/<80 to <129/<80 for children ≥13 years	<25%
White coat hypertension	Age <13 years: ≥95th percentile Age ≥13 years: >120/<80 mm Hg	Age <13 years: <90th percentile Age ≥13 years: <120/<80 mm Hg	<25%
Masked hypertension	Age <13 years: <90th percentile Age ≥13 years: <120/<80 mm Hg	Age <13 years: ≥95th percentile Age ≥13 years: >120/<80 mm Hg	>25%
Ambulatory hypertension	Age <13 years: ≥95th percentile Age ≥13 years: >130/>80 mm Hg	Age <13 years: ≥95th percentile Age ≥13 years: >130/>80 mm Hg	25%–50%
Severe ambulatory hypertension (at risk for end-organ damage)	All ages: ≥95th percentile + 12 mm Hg	All ages: ≥95th percentile + 12 mm Hg	>50%

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a] Derived from Flynn JT, Daniels SR, Hayman LL, et al. Update: ambulatory blood pressure monitoring in children and adolescents. *Hypertension*. 2014;63(5):1116–1135.

[b] SBP load % is defined as number of SBP readings above the normal value divided by the total number of blood pressure readings × 100.

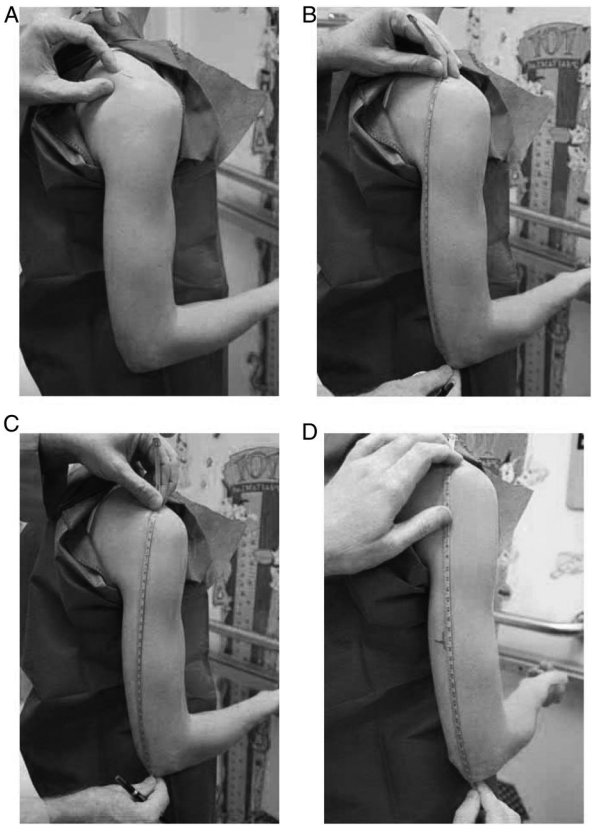

Figure 106.1. Determining the proper cuff size in the pediatric patient. A, Marking the scapula extending from the acromion process. B, Correct tape placement for upper arm length. C, Incorrect tape placement for upper arm length. D, Marking upper arm length at the midpoint.

Reprinted with permission from Flynn JT, Kaelber DC, Baker-Smith CM, et al; American Academy of Pediatrics Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904.

Table 106.7. Blood Pressure Cuff Size Chart

Age Range	*Width (cm)*	*Length (cm)*	*Maximum Arm Circumference (cm)*[a]
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small adult	10	24	26
Adult	13	30	34
Large adult	16	38	44
Thigh	20	42	52

[a] Calculated so that the largest arm would still allow bladder to encircle arm by at least 80 percent.

Reprinted with permission from National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services. *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.* Washington, DC: National Heart, Lung, and Blood Institute; May 2005. NIH publication 05–5267.

Various methods of monitoring BP are used in pediatric practice, including manual auscultatory aneroid sphygmomanometers and oscillometric automated devices, the latter of which use mean arterial pressure to calculate systolic and diastolic BP. The pediatrician should ensure that all devices are validated for pediatric ages using a resource such as www.dableducational.org. Oscillometric devices are known to correlate significantly with arterial BP, although a tendency exists for higher systolic and slightly higher diastolic pressures with portable devices. Therefore, according to the 2017 AAP CPG, after obtaining a BP reading with elevated BP using an automated oscillometric device, BP measurements must be repeated twice more and an average of the measurements calculated. If the BP remains elevated, the BP should be confirmed using a manual auscultatory aneroid device.

Epidemiology

Based on the current definition of persistent HTN in children, the prevalence of HTN in the pediatric population is approximately 4% to 5%; however, the prevalence of HTN is 10% in children with elevated BP who are at risk for HTN. Hypertension can vary depending on patient factors such as age, ethnicity, and geographic distribution as well as type of HTN. Recent data suggest that the overall prevalence of HTN has decreased among children of normal weight in the past decade. Among children with obesity, however, recent studies indicate that the prevalence of HTN is between 2- and 5-fold, compared with children of normal weight. Prevalence of HTN varies by the study population and the age group studied. Hypertension in pediatrics remains a major health issue because of increasing prevalence of obesity, survival of preterm infants, and cultural and lifestyle changes, including increases in stress and sedentary behavior. As in adults, HTN is more common among black and Hispanic children compared with white children. Furthermore, adolescents and those from urban areas tend to have higher prevalence of HTN compared with younger children and those from rural areas. Recent evidence has also shown that parental socioeconomic status is a risk factor for development of HTN in childhood, with low income populations disproportionately affected. Primary care providers should recognize at-risk patient populations to identify HTN promptly and treat it appropriately to avoid long-term cardiovascular complications.

Secondary HTN is more common among infants and young children and is associated with other conditions, including most commonly renal and/or renovascular disease. Secondary HTN also can be caused by cardiovascular disease, such as coarctation of aorta or prior surgical repair of cardiovascular lesions, endocrine disorders, or environmental exposures. Children who require hospital admission for HTN usually have secondary HTN, which may have been triggered by an acute event—often volume overload.

Occasionally, the cause of HTN is uncertain. In many such children, the acutely increased BP resolves with appropriate medical intervention, and most children do not require long-term treatment. What is certain, however, is that essential HTN in childhood increases the risk for adult HTN and metabolic syndrome.

Etiology and Pathophysiology

An increase in BP results from an increase in peripheral resistance or cardiac output or a combination of these. In 90% to 95% of adults, the precise cause of HTN is uncertain; hence, the term essential, primary, or idiopathic HTN. Historically, HTN was considered secondary to an underlying disorder in more than 80% of children, and fewer than 20% of cases were idiopathic; however, this was true only in children with very severe HTN. Adolescents with obesity and mildly elevated BP in whom no etiology of HTN is identified often have a family history of HTN and are classified as having essential HTN.

Many factors play a role in the development of essential HTN. Research reveals variable degrees of alteration in cardiac output, extracellular fluid volume, peripheral resistance, renin-angiotensin system, aldosterone, electrolyte balance, catecholamines, sympathetic nervous system, natriuretic hormones, prostaglandins, kinins, antidiuretic hormone, insulin response, endothelin, nitric oxide (ie, endothelium-derived relaxing factor), and others. Whether these abnormalities are primary or secondary and what their exact role is in the pathogenesis of essential HTN remains uncertain.

Additionally, several maternal factors, such as smoking, alcohol consumption, diet, obesity, diabetes, and hypothyroidism/hyperthyroidism may influence epigenetic pathways. Epigenetic changes occur as a result of methylation or acetylation of the noncoding gene segment (ie, histones) that can change the chromosomal configuration and result in activation or inhibition of a specific gene transcription (ie, turning the gene on or off), which may result in abnormal developmental. This hypothesis has been further supported by data demonstrating an association between fewer nephrons (resulting from underexpression of genes responsible for branching) in children who were born small for gestational age and later developed HTN. Thus, it is quite important to optimize maternal health to prevent potentially long-term adverse effects on the fetus.

Other important factors in the development of HTN include ethnicity, heredity, stress response, sleep apnea, obesity, hyperlipidemia, and increased salt intake. Studies showing that weight reduction in patients with obesity results in reduced BP strengthen the argument that obesity contributes to HTN.

Secondary HTN is more likely to exist in very young children with HTN, those who meet the criteria for stage 2 HTN, and those with systemic symptoms of HTN. The etiology of secondary HTN varies based on patient age and the nature of the HTN, that is, whether the condition is acute or chronic. Renal abnormalities account for 70% to 80% of secondary HTN in children. The pathogenesis of the HTN may be related to an increase in extracellular fluid volume (eg, acute glomerulonephritis, chronic renal failure), an increase in renin-angiotensin II activity (eg, renal artery stenosis, renin-producing tumor, pheochromocytoma, reflux nephropathy), or a combination of both mechanisms (eg, a patient with chronic renal failure caused by reflux nephropathy). Additionally, in young children, HTN may rarely be caused by a disorder with a single gene mutation that affects different pathways related to renal sodium handling.

Clinical Presentation

In most children, elevated BP, white coat HTN, masked HTN, and stage 1 HTN usually are asymptomatic. With stage 2 HTN, however, a child can develop headache or blurring of vision and, less commonly, nosebleed, changes in mental status, vomiting, and cardiac complaints (eg, chest pain, palpitations). Acute presentations of HTN are divided into 2 categories: hypertensive urgency and hypertensive emergency. *Hypertensive urgency* is defined by the sudden development of elevated BP without evidence of severe end-organ damage or life-threatening symptoms but may present with more mild symptoms, such as headache and vomiting. A *hypertensive emergency,* often called *hypertensive crisis,* in comparison, is defined by obvious signs of significant end-organ damage and life-threatening symptoms, such as encephalopathy, seizure, papilledema, retinal hemorrhage, and kidney injury. In children, these conditions usually are caused by secondary HTN rather than primary HTN. Cases of hypertensive urgency and hypertensive emergency both warrant immediate evaluation and referral to an emergency department for treatment.

Differential Diagnosis

An effort should be made to identify the cause of HTN in all young children because only 30% of them are likely to have essential HTN. In older children and adolescents with mildly elevated BP, essential HTN is the most likely diagnosis. In the setting of stage 1 or 2 HTN, however, a detailed history, complete physical examination, and simple laboratory tests to identify etiology should be completed (Boxes 106.1 and 106.2).

Evaluation

Blood pressure measurement should be part of the annual routine physical examination for all children older than 3 years and for all hospitalized children. If BP is normal in the annual examination, routine BP measurements between that examination and the next annual examination are not required. Regardless of age, however, all children with risk factors such as history of prematurity, congenital heart disease, recurrent urinary tract infections, renal disease, or chronic systemic illnesses, should undergo BP measurement as a routine part of every visit.

The physician also should verify that an appropriately sized cuff is being used for BP measurement and that efforts have been made to put the child at ease. Many children develop mild increases of BP (which can extend into the hypertensive range) when they visit a doctor's office because of anxiety or apprehension (ie, white coat HTN). In the patient with a BP measurement in the elevated, stage 1, or stage 2 HTN ranges, BP should be reassessed with at least 2 additional measurements in the same clinic visit by oscillometric or auscultatory BP and the values averaged. If the averaged BP remains elevated based on oscillometric technique alone, BP should be remeasured twice by auscultation with stethoscope and appropriate sphygmomanometer by a trained professional to confirm the reading.

Box 106.1. Causes of Acute or Intermittent Increases in Blood Pressure in Children

Renal
- Acute glomerulonephritis
- Hemolytic uremic syndrome
- Henoch-Schönlein purpura nephritis
- Renal trauma
- Renal artery or vein thrombosis
- After renal biopsy
- Acute obstructive uropathy
- After genitourinary surgery
- Blood transfusion in the patient with renal failure
- After kidney transplant or with transplant rejection

Drug-induced
- Corticosteroids
- Amphetamine overdose
- Phencyclidine hydrochloride overdose
- Cocaine overdose
- Anabolic steroids
- Oral contraceptives
- Excessive erythropoietin use in the patient with end-stage renal disease
- Cyclosporine A and tacrolimus

Central Nervous System
- Increased intracranial pressure (eg, subdural hematoma, meningitis, tumors)
- Encephalitis
- Poliomyelitis
- Guillain-Barré syndrome
- Porphyria
- Familial dysautonomia

Miscellaneous
- Wrong blood pressure cuff size
- Anxiety, apprehension (ie, white coat hypertension)
- Pain
- Fracture
- Immobilization
- Orthopedic procedures, especially leg lengthening and those requiring traction
- Abdominal wall defect
- Burns
- Leukemia
- Stevens-Johnson syndrome
- Bacterial endocarditis
- Hypernatremia
- Hypercalcemia
- Heavy metal poisoning

Box 106.2. Causes of Chronic Hypertension in Children

Renal
- Scarred kidney resulting from pyelonephritis or vesicoureteral reflux nephropathy
- Chronic glomerulonephritis
- Connective tissue disease (ie, systemic lupus erythematosus, Henoch-Schönlein purpura)
- Hydronephrosis
- Renal dysplasia, multicystic dysplastic kidney
- Polycystic kidney disease
- Solitary renal cyst
- Tumors (ie, Wilms, hemangiopericytoma [renin-producing])

Renal Vascular Lesions
- Renal artery stenosis (ie, fibromuscular dysplasia)
- Renal artery thrombosis, especially in the newborn after umbilical artery catheterization
- Renal vein thrombosis
- Renal artery lesions with neurofibromatosis, tuberous sclerosis

Other Vascular Lesions
- Coarctation of aorta (ie, thoracic, abdominal)
- Polyarteritis nodosa and other vasculitic disorders

Endocrine
- Corticosteroid treatment
- Neuroblastoma or other neural crest tumors
- Pheochromocytoma
- Congenital adrenal hyperplasia with 11-β-hydroxylase deficiency or 17-α-hydroxylase deficiency
- 11-β-hydroxysteroid dehydrogenase deficiency
- Liddle syndrome
- Primary aldosteronism
- Dexamethasone-suppressible hyperaldosteronism
- Hyperthyroidism
- Hyperparathyroidism
- Cushing syndrome

Central Nervous System
- Intracranial hemorrhage
- Intracranial mass
- Sleep apnea/disordered breathing

Essential (Primary) Hypertension

The most recent AAP CPG recommends that, if available, ABPM should be performed for confirmation of HTN in children and adolescents with office BP measurements in the elevated BP category for more than 1 year or with stage 1 HTN over the course of 3 clinic visits to confirm diagnosis. Ambulatory BP monitoring may also help identify masked HTN or an elevated BP state in a child by detecting the usual nocturnal dips in BP. Additionally, routine performance of ABPM should be strongly considered in the child or adolescent with a high-risk condition, such as a history of repaired coarctation of aorta, chronic kidney disease, obstructive sleep apnea, type 1 or 2 diabetes, heart transplant, or kidney transplant. In these select patients, ABPM is performed to assess HTN severity and determine if the circadian BP pattern is abnormal, which may be the first sign

of a BP disorder and an increased risk for target organ damage. Additionally, in the patient in whom white coat HTN or masked HTN is suspected, ABPM is the only reliable measure that could confirm either condition. Furthermore, ABPM can help identify whether the child's blood pressure returns to normal during sleep. Failure of the blood pressure to decrease overnight indicates a pathological basis for the hypertension.

Despite the benefits of ABPM, the apparatus is cumbersome, the study is costly, and sleep may be disturbed by the cuff inflation, thereby influencing the results. Additionally, few outpatient clinics have access to ABPM and insurance may not cover the test. Ambulatory BP monitoring requires trained technicians to effectively place devices and extract data. As an alternative to ABPM, home BP monitoring 3 times a day for 7 days with accurate logging can be done. Blood pressure devices used at home should be evaluated in the clinic for accuracy and validation for a pediatric population. Some studies have shown home monitoring to be as effective as ABPM, and home monitoring is currently used by many practitioners. Therefore, home or school BP monitoring should be considered as an alternative to ABPM.

History

The history is the first step in evaluating the etiology of elevated BP. Information should be obtained about symptoms that may be associated with HTN, such as headaches and visual difficulties (Box 106.3). The physician should also inquire about duration of gestation, birth weight, prenatal and perinatal complications, use of umbilical artery catheterization, unexplained fevers during infancy and early childhood, previous urinary tract infections, dark urine, bed-wetting, swelling of extremities, and renal disease. Additionally, the physician should elicit information about the child's physical growth, BP recordings during previous physical examinations, eating and nutritional habits (especially salt intake), use of drugs (including illicit drug use), and family history of HTN and renal disease.

Physical Examination

A thorough physical examination is essential for determining the etiology of HTN and the extent of target organ damage. Poor physical growth or short stature may be indicative of an underlying condition, such as Turner syndrome or chronic renal disease with or without renal failure; it may also be the consequence of long-standing severe HTN alone. Fundus examination is diagnostic for whether HTN has been severe and chronic, resulting in arterial changes, exudate, hemorrhages, or papilledema. Tachycardia may be indicative of heart failure or thyrotoxicosis. The child's pulses should be palpated in the upper and lower extremities, and BP should be measured in all 4 extremities to evaluate for coarctation of aorta and other vascular lesions.

A heart murmur may be detected in the patient with coarctation of aorta. Some patients may present in heart failure secondary to chronic severe HTN or renal disease with fluid retention. Abdominal examination may reveal the presence of masses caused by cystic kidney, Wilms tumor, or neuroblastoma or tenderness, especially in the costovertebral angle. Bruits sometimes may be heard anteriorly, over the lower portions of the left or right upper quadrants in patients with renal artery stenosis. The presence of café au lait or depigmented spots on the skin may be secondary to neurofibromatosis or tuberous sclerosis, respectively, and may contribute to HTN.

Box 106.3. What to Ask

Hypertension

- Does the child have any symptoms associated with hypertension (eg, headache, dizziness, nosebleed, visual difficulty, shortness of breath)?
- Have blood pressure readings been obtained during previous routine physical examinations?
- Has the child had any hematuria, generalized swelling of the body (ie, edema), enuresis (eg, nocturia), burning urination, previous urinary tract infection, or other kidney problems?
- How much salt does the child ingest? Does the child routinely add extra salt on most foods and frequently like to eat salty foods?
- How has the child been growing?
- Does a history exist of use of illicit drugs or oral contraceptives?
- Does a family history exist of hypertension, renal disease, autoimmune disorders, or endocrine diseases?

Laboratory Tests

The extent of laboratory evaluation depends on clinical findings, the nature of the HTN (eg, stage 1 or 2, acute or chronic), and whether an etiology is apparent or obscure. Laboratory studies can be done in 3 phases to minimize unnecessary cost and patient discomfort. Box 106.4 lists suggested laboratory workups for patients with stage 1 or 2 HTN.

The presence of hematuria, heavy proteinuria, pyuria, or elevated blood urea nitrogen or plasma creatinine is clearly indicative of a renal disorder as the cause of HTN and warrants appropriate renal evaluation. A kidney biopsy should be performed to diagnose glomerulonephritis, and radiologic investigations, such as ultrasonography and nuclear medicine scintigraphy, can help identify scarred kidney, hydronephrosis, cystic kidney, or tumor.

The presence of electrolyte abnormalities, such as hypokalemia, hypochloremia, and metabolic alkalosis, is indicative of increased mineralocorticoid hormone activity on a primary or secondary basis (Box 106.5). Endocrine-based causes of HTN in children are uncommon, and tests such as plasma or urinary fractionated metanephrines and catecholamines, plasma cortisol, thyroid-stimulating hormone, and triiodothyronine are indicated based on the clinical evaluation to diagnosis neuroendocrine tumors, Cushing syndrome or disease, or hyperthyroidism, respectively (Box 106.2).

Imaging Studies

Currently, the AAP CPG recommendation is that echocardiography should be performed at the time of initiation of pharmacotherapy for the management of HTN. In several studies, LVH is present even in children with untreated mild, white coat, or masked HTN, especially in children with overweight. In such cases in which signs of cardiac involvement exist, echocardiography should be considered.

Newer recommendations also include obtaining sleep studies in patients with overweight to evaluate for obstructive sleep apnea, which can contribute to the development of HTN and LVH. Evidence suggests that with appropriate treatment to improve sleep apnea, BP normalizes and end-organ damage is prevented.

Box 106.4. Laboratory and Radiologic Evaluation of Stage 1 or 2 Hypertension in the Pediatric Patient

Phase 1: Initial Evaluation (To Identify Common Causes of Hypertension and Evaluate for Cardiac End-Organ Damage)

1. Urinalysis (urine culture if indicated)
2. Complete blood cell count, serum electrolytes, blood urea nitrogen, and creatinine; lipid profile, liver profile, and hemoglobin A_{1C} for patients with obesity
3. Urine toxicology screening in adolescent patients

Phase 2: More Extensive Evaluation (To Rule Out Rare Causes of Hypertension)

1. Calcium, phosphorus, and PTH
2. Plasma renin activity and plasma aldosterone, cortisol, and TSH
3. Plasma fractionated catecholamines and metanephrines
4. Renal Doppler ultrasonography
5. Enalapril- or captopril-enhanced Tc 99m mertiatide renal scintigraphy
6. Renal arteriography (selective if necessary)
7. Echocardiography at any point before starting pharmacologic treatment

Phase 3: Identify Specific Etiologies (Studies Done Mostly by Specialists)

1. Diuretic renal scintigraphy, DMSA scintigraphy, or voiding nuclear cystography
2. Renal biopsy
3. Specific imaging studies, including nuclear scintigraphy to rule out pheochromocytoma or neuroblastoma
4. 24-hour urine HVA and VMA (obtain only if plasma fractionated catecholamines and metanephrines are >5 times higher than the normal range)
5. Other endocrine, neurology, or cardiology studies

Abbreviations: DMSA, 99mTc dimercaptosuccinic acid; HVA, homovanillic acid; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; VMA, vanillylmandelic acid.

Box 106.5. Disorders Associated with Abnormal Electrolytes

Primary Basis

- Primary aldosteronism
- Glucocorticoid remediable aldosteronism
- Adrenogenital syndrome with 11-β-hydroxylase deficiency or 17-α-hydroxylase deficiency
- Liddle syndrome
- 11-β-hydroxysteroid dehydrogenase deficiency
- Apparent mineralocorticoid excess

Secondary Basis

- Renovascular hypertension
- Renin-producing tumor
- Reflux nephropathy

If the history, physical examination, and initial investigation do not reveal the etiology of severe HTN, renovascular disease should be considered and plasma renin activity and aldosterone level should be obtained and renal Doppler ultrasonography performed (Box 106.4). In the patient with suspected narrowing of the renal artery, however, interventional renal angiography is the standard for both diagnostic and therapeutic purposes should a patient require angioplasty or stent placement during the study.

Gene Studies

Gene studies are rarely indicated but should be considered in young children with markedly elevated BP, signs of end-organ damage, and findings suggestive of a single gene-related condition. A positive study is diagnostic; however, a negative result does not exclude an underlying genetic disorder. With advancement in the field, more commercial tests to diagnosis genetic etiologies of HTN are available, and it is crucial that pediatricians use these tests to optimize management, particularly in a very young child in whom a genetic form of HTN is suspected.

Management

Management is predicated on identifying the cause of the HTN. Initial treatment of the patient with elevated BP should be conservative, consisting of lifestyle modifications, including a healthy and well-balanced diet that is low in sodium and rich in fruits and vegetables. Additionally, the patient should be encouraged to optimize sleep. Nutrition and/or weight management referrals should be considered when appropriate. The patient with elevated BP should be followed up within 3 to 6 months. If BP normalizes, annual well-child care visits may be resumed. If the patient has persistent elevated BP for greater than 12 months, however, a diagnostic evaluation should be conducted and the patient referred to a specialist in cardiology or nephrology.

The child with stage 1 HTN initially may be managed with nonpharmacologic measures unless the patient is symptomatic or has significant cardiovascular risk factors (eg, diabetes, hyperlipidemia) and has a strong family history of HTN, stroke, or myocardial infarction at a young age. These measures include supportive care, reduction in sodium intake to approximately less than 2 g a day, weight reduction if the child has obesity, and use of biofeedback. The latter may consist of basic relaxation techniques, such as yoga or mediation, or more advance measures, such as thermal biofeedback accomplished by adjusting skin temperature, electromyography to release muscle tension, or neurofeedback focusing on electrical brain activity, most of which are in-facility programs.

The primary care physician is in an ideal position to help children achieve target BP and weight and protect against long-term cardiovascular complications. Promoting healthy cardiovascular exercise with concrete, attainable goals in addition to providing optimal diet plans that are culturally and socioeconomically appropriate to the individual child and family are crucial to empowering children and their families. Although every community is unique, primary care physicians should become familiar with local resources to assist patients, including available dietitians, social workers, and local health care organizations.

The child with stage 1 HTN should be reevaluated 1 to 2 weeks after the initial reading with 4-extremity BP measurements and

peripheral pulse evaluation. If after a 3- to 6-month observation period or 3 clinic visits with BP persistently in stage 1 HTN, pharmacologic treatment should be initiated and the physician should give consideration to performing a more thorough laboratory evaluation.

Drug therapy may begin with a beta blocker (eg, atenolol), a calcium channel blocker (eg, amlodipine besylate, isradipine), an angiotensin-converting enzyme inhibitor (eg, enalapril), an angiotensin II blocker (eg, losartan potassium), or a diuretic agent (eg, hydrochlorothiazide) (Table 106.8). Risk factors must be taken into consideration when instituting a treatment plan. For example, the child with obesity who has a family history of HTN may also have chronic kidney disease. In such a case, treatment should be

Table 106.8. Recommended Doses for Select Antihypertensive Agents for Use in Children and Adolescents With Hypertension

Class	*Drug*	*Starting Dose*	*Interval*	*Maximum Dose**
Angiotensin-converting enzyme inhibitors	Benazepril**	0.2 mg/kg/day up to 10 mg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Captopril**	0.3–0.5 mg/kg/dose	BID-TID	6 mg/kg/day up to 450 mg/day
	Enalapril**	0.08 mg/kg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Fosinopril	0.1 mg/kg/day up to 10 mg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Lisinopril**	0.07 mg/kg/day up to 5 mg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Quinapril	5–10 mg/day	QD	80 mg/day
	Ramipril	2.5 mg/day	QD	20 mg/day
Angiotensin-receptor blockers	Candesartan	4 mg/day	QD	32 mg/day
	Irbesartan	75–150 mg/day	QD	300 mg/day
	Losartan**	0.75 mg/kg/day up to 50 mg/day	QD	1.4 mg/kg/day up to 100 mg/day
α- and β-adrenergic antagonists	Labetalol**	2–3 mg/kg/day	BID	10–12 mg/kg/day up to 1.2 g/day
	Carvedilol	0.1 mg/kg/dose up to 12.5 mg BID	BID	0.5 mg/kg/dose up to 25 mg BID
β-adrenergic antagonists	Atenolol**	0.5–1 mg/kg/day	QD-BID	2 mg/kg/day up to 100 mg/day
	Bisoprolol/HCTZ	0.04 mg/kg/day up to 2.5/6.25 mg/day	QD	10/6.25 mg/day
	Metoprolol	1–2 mg/kg/day	BID	6 mg/kg/day up to 200 mg/day
	Propranolol	1 mg/kg/day	BID-TID	16 mg/kg/day up to 640 mg/day
Calcium channel blockers	Amlodipine**	0.06 mg/kg/day up to 5 mg/day	QD	0.6 mg/kg/day up to 10 mg/day
	Felodipine	2.5 mg/day	QD	10 mg/day
	Isradipine**	0.05–0.15 mg/kg/dose	TID-QID	0.8 mg/kg/day up to 20 mg/day
	Extended-release nifedipine	0.25–0.50 mg/kg/day	QD-BID	3 mg/kg/day up to 120 mg/day
Central α-agonists	Clonidine**	5–10 mcg/kg/day	BID-TID	25 mcg/kg/day up to 0.9 mg/day
	Methyldopa**	5 mg/kg/day	BID-QID	40 mg/kg/day up to 3 g/day
Diuretics	Amiloride	5–10 mg/kg/day	QD	20 mg/day
	Chlorothiazide	10 mg/kg/day	BID	20 mg/kg/day up to 1.0 gram/day
	Chlorthalidone	0.3 mg/kg/day	QD	2 mg/kg/day up to 50 mg/day
	Furosemide	0.5–2.0 mg/kg/dose	QD-BID	6 mg/kg/day
	HCTZ	0.5–1 mg/kg/day	QD	3 mg/kg/day up to 50 mg/day
	Spironolactone**	1 mg/kg/day	QD-BID	3.3 mg/kg/day up to 100 mg/day
	Triamterene	1–2 mg/kg/day	BID	3–4 mg/kg/day up to 300 mg/day
Peripheral α-antagonists	Doxazosin	1 mg/day	QD	4 mg/day
	Prazosin	0.05–0.1 mg/kg/day	TID	0.5 mg/kg/day
	Terazosin	1 mg/day	QD	20 mg/day
Vasodilators	Hydralazine	0.25 mg/kg/dose	TID-QID	7.5 mg/kg/day up to 200 mg/day
	Minoxidil	0.1–0.2 mg/kg/day	BID-TID	1 mg/kg/day up to 50 mg/day

BID, twice-daily; HCTZ, hydrochlorothiazide; QD, once-daily; QID, four times daily; TID, three times daily.

* The maximum recommended adult dose should not be exceeded.

** Information on preparation of a stable extemporaneous suspension is available for these agents.

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undertaken not only in an attempt to control BP using medications appropriate for a patient with kidney disease but also for weight reduction, dietary modifications, and increased physical activity. For the adolescent who smokes cigarettes, cessation of smoking is essential as well.

For the patient with asymptomatic stage 2 HTN, laboratory and diagnostic studies and a nephrology or cardiology referral should be done within 1 week, but ideally, within a few days of documenting stage 2 HTN. When possible, the pediatrician should contact the specialist by email or telephone to obtain advice about the immediate need to initiate treatment. In addition to lifestyle modification, combination therapy or the use of additional drugs, such as alpha blockers (eg, prazosin hydrochloride), alpha and beta dual receptor blockers (eg, labetalol hydrochloride), peripheral vasodilators (eg, hydralazine hydrochloride, minoxidil), or centrally acting drugs (eg, clonidine) is recommended (Table 106.8). The use of 1 or more of these drugs controls BP in most patients within a satisfactory range with a limited number of side effects. Patients with renal artery stenosis can be successfully treated with balloon dilatation or stent placement. If the procedure is unsuccessful or stenosis recurs, surgical correction is usually successful.

If a patient develops any signs of severe neurologic or cardiac symptoms, or has BP greater than 30 mm Hg above the 95th percentile (ie, >180/120 mm Hg in an adolescent), immediate referral to an emergency department for evaluation and treatment is mandatory. Hypertensive emergencies require rapid intervention with intravenous medications, such as labetalol hydrochloride, nicardipine hydrochloride, or sodium nitroprusside. Hypertensive urgencies may be managed initially with the aforementioned intravenous medications, oral labetalol hydrochloride, or an angiotensin-converting enzyme inhibitor. In either hypertensive emergencies or urgencies, the goal is to reduce the BP by approximately 20% to 25% of the presenting values in the first 8 hours. In the following days to weeks, BP is gradually reduced to within normal values. According to the AAP CPG, the goal of intervention for patients with HTN is BP less than the 90th percentile or less than 130/80 mm Hg.

Management of HTN must involve the patient's family. A holistic approach with the family and consideration of socioeconomic, behavioral, nutritional, and cultural factors provides the most effective treatment.

Prognosis

The long-term outcome of HTN in the pediatric patient depends on the underlying etiology. In the child or adolescent with severe HTN, BP control improves growth and overall well-being. The very long-term (ie, 40- to 50-year) prognosis for the child with persistent, mild essential HTN is largely unknown; however, adequate BP control should prolong life and reduce cardiovascular, central nervous system, renal, and retinal morbidity. In untreated or poorly controlled HTN the prognosis is poor. The prognosis is significantly worse in patients with poorly controlled HTN and obesity and hyperlipidemia, which is associated with severe cardiovascular morbidity and mortality in adults.

Prevention

Although no specific predictors exist for the development of HTN later in life, it is likely that early childhood health plays a role. Children who are small at birth and undergo rapid catch-up growth seem to have a higher incidence of obesity and HTN later in life. Overall, infants fed mother's milk have lower rates of HTN as adults. As a result, it has been postulated that encouraging breastfeeding may have a protective effect. It is important to be aware that preterm and small for gestational age infants are often given high-density carbohydrate and lipid supplements for rapid weight gain. Studies have shown that rapid weight gain during the first 2 years after birth correlates strongly with adverse cardiovascular health in adulthood. Later in life, limiting intake of sodium and caffeine may reduce rates of HTN in adolescents. Programs aimed at preventing childhood obesity likely will prevent HTN as well.

CASE RESOLUTION

Because of the elevated BP and evidence of end-organ dysfunction (ie, LVH), the patient is diagnosed as having stage 2 essential HTN. Her history of prematurity raises the possibility of renal artery thrombosis or stenosis secondary to umbilical artery catheter. First, dietary modifications (ie, diet low in refined sugar and sodium) and increasing physical activity should be addressed. Second, because the patient has evidence of LVH and early changes of retinopathy, appropriate antihypertensive medication to control the BP should be initiated. A calcium channel blocker or beta blocker can be used. Renal Doppler ultrasonography is appropriate to determine kidney size, extent of kidney damage, and blood flow to the kidneys.

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PART 9

Genitourinary Disorders

CHAPTER 107

Disorders of Sexual Differentiation

Jennifer K. Yee, MD, and Catherine S. Mao, MD

CASE STUDY

A term neonate is being evaluated in the newborn nursery. The mother received prenatal care from the eighth week of gestation, reportedly had no problems during the pregnancy, and took no medications except prenatal vitamins with iron. She specifically denies taking any progesterone-containing drugs. Her previous pregnancy was uneventful, and her 3-year-old son is healthy.

On physical examination, the newborn is active and alert, with normal vital signs. Aside from a minimum amount of breast tissue bilaterally, the physical examination is unremarkable, except for the genitalia. The labioscrotal folds are swollen bilaterally with slight hyperpigmentation and mild rugae. No masses are palpable in the labioscrotal folds. The clitoris/phallus is 1.5 cm in length. Labioscrotal fusion is present, with a very small opening at the anterior aspect. The urethra cannot be visualized.

Questions

1. What conditions should be considered in the newborn with a disorder of sexual differentiation?
2. What should the family of a newborn with a disorder of sexual differentiation be told about the sex of the newborn?
3. What key historical information should be obtained from the family of the newborn with a disorder of sexual differentiation?
4. What laboratory studies must be obtained to aid in the diagnosis?
5. What psychosocial issues should be addressed with the family while the neonate is in the newborn nursery?

Disorders of sexual differentiation (DSDs) in newborns can result in ambiguous genitalia and are classified according to chromosomal status and gonads present. This standard classification, using newer nomenclature with previously used nomenclature in parentheses, includes 46,XX DSD (ie, female pseudohermaphroditism), 46,XY DSD (ie, male pseudohermaphroditism), ovotesticular DSD (ie, true hermaphroditism), and 46,XX testicular DSD or 46,XY gonadal dysgenesis (ie, complete or mixed gonadal dysgenesis). Gonadal dysgenesis in 45,X and 46,XX individuals does not present with ambiguous genitalia but is also classified as a DSD.

A multidisciplinary team should be involved in the care of the newborn with a DSD. In addition to the general pediatrician, significant members of the team include nurses, social workers, neonatologists, pediatric endocrinologists, geneticists, and surgeons. The role of the primary care physician cannot be underestimated, however, because this professional is always involved in the initial evaluation of the newborn and often has an established relationship with the family.

Epidemiology

The prevalence of ambiguous genitalia in newborns is approximately 1 in 3,000 to 4,000 live births. The 46,XX DSD is characterized by female chromosomes (46,XX), normal ovaries and müllerian structures, and virilized external genitalia. The most common DSD—46,XX DSD—is most often caused by congenital adrenal hyperplasia (CAH). Neonatal screening studies suggest that the incidence of CAH is 1 in 5,000 to 15,000 live births per year.

The 46,XY DSD occurs in genetic males (46,XY) who have testes but with insufficient masculinization of the external genitalia. This disorder most commonly results from androgen insensitivity. Ovotesticular DSD is a rare condition in which ovarian and testicular tissues are present. Seventy percent to 80% of affected individuals have the 46,XX karyotype, and the morphology of the external genitalia varies widely.

The 46,XY gonadal dysgenesis is characterized by ambiguous genitalia or a female phenotype with a normal XY karyotype. The affected neonate may have a specific gene abnormality that results in abnormal testicular development and often streak gonads. Reports indicate that this condition is the second most common form of ambiguous genitalia. The affected newborn with chromosomal mosaicism (45,X/46,XY) is considered to have mixed gonadal dysgenesis.

Clinical Presentation

Variability in the phenotypic and clinical presentation of these disorders is considerable (Box 107.1). The newborn with DSD with ambiguous genitalia may have an enlarged clitoris or small phallus and varying degrees of labioscrotal fusion. Signs of virilization

Box 107.1. Diagnosis of Disorders of Sexual Differentiation

- Indeterminate or ambiguous genitalia
- Enlarged clitoris or small phallus
- Hyperpigmented, rugated labia majora that may be fused
- Blind-ending or absent vaginal pouch
- Phenotypic male neonate with hypospadias or bilateral cryptorchidism
- Phenotypic female neonate with an inguinal hernia or mass

in the female newborn might include hyperpigmented labia and presence of labial rugae. Other findings suggestive of 46,XX DSD are perineal hypospadias or an inguinal hernia. More dramatic presentations, such as severe dehydration and shock in a neonate, are associated with CAH of the salt-wasting form. Females with gonadal dysgenesis often present in adolescence with primary amenorrhea (see Chapter 61). Turner syndrome (45,XO) is a common cause of gonadal dysgenesis and may present with additional clinical features; 46,XX "pure" gonadal dysgenesis is a distinct entity.

Pathophysiology

To appropriately evaluate and interpret laboratory results of the neonate with ambiguous genitalia, it is important to understand the physiology of sexual differentiation and how deviations from this process result in DSD.

Normal Sexual Differentiation

Before an embryo reaches 6 weeks, germ cells migrate from the yolk sac into the undifferentiated bilateral gonads. Both wolffian and müllerian duct systems are present, and the embryonic gonads of males and females are indistinguishable at this time.

If a Y chromosome is present, a testes-determining factor known as sex-determining region Y (SRY) induces differentiation of these gonads into testes by stimulating *SOX9* (SRY-related gene) expression in the gonads, thus blocking female development. This process involves the formation of seminiferous tubules that surround the germ cells. Leydig cells begin to produce testosterone, which in turn acts on the wolffian duct to result in male internal genitalia: vas deferens, epididymis, and seminal vesicles. Concurrently, *SOX9* acts with steroidogenic factor 1, resulting in regression of the müllerian ducts secondary to Sertoli cell production of anti-müllerian hormone, also known as müllerian-inhibiting substance. The formation of normal male external genitalia is dependent on the conversion of testosterone to dihydrotestosterone (DHT) via 5-α-reductase. Dihydrotestosterone then combines with a specific androgen receptor, which allows formation of the phallus and scrotum from the previously undifferentiated external genitalia. The process primarily involves growth and fusion. Later in gestation, the testes migrate into the scrotum.

The development of undifferentiated gonads into female organs is dependent on the absence of the Y chromosome and the presence of 2 intact and normal functioning X chromosomes. Because androgens are not produced and anti-müllerian hormone is not present, the wolffian duct degenerates and the müllerian duct develops into the internal female structures: fallopian tubes, uterus, and upper vagina. Fusion of undifferentiated external genitalia does not occur in the absence of DHT; thus, the external genitalia develops into the labia, and the genital tubercle becomes the clitoris. Female differentiation was previously believed to be the default development in the absence of SRY; however, recent studies support the existence of female determining factors (ie, R-spondin1 and Wnt signaling molecule Wnt4).

Disorders of Sexual Differentiation

Congenital adrenal hyperplasia is the most common cause of virilization of the female and is an autosomal recessively inherited defect. Congenital adrenal hyperplasia is the result of an enzymatic deficiency in the pathway for synthesis of cortisol and aldosterone from cholesterol. The most common of these enzymatic defects is 21-α-hydroxylase deficiency. Other less common defects are 11-β-hydroxylase deficiency and 3-β-hydroxysteroid dehydrogenase deficiency. Lipoid adrenal hyperplasia results from a defect in the steroidogenic acute regulatory (StAR) protein enzyme that transports cholesterol across the mitochondrial membrane for steroid synthesis. A rare form of CAH is cytochrome P-450 oxidoreductase deficiency, which can be associated with Antley Bixler syndrome. Prenatally, circulating levels of androgens are abnormally high from the overproduction of precursors in the steroid synthesis pathways. As a result, the external genitalia of the fetus, which are controlled by androgens, are virilized in the female. Internal female organs, however, are normal because their development is not influenced by androgens. Males with the common forms of CAH (21-α-hydroxylase and 11-β-hydroxylase deficiency) may exhibit hyperpigmentation and increased rugosity but otherwise have normal external genitalia.

Approximately two-thirds of patients with classic CAH resulting from 21-α-hydroxylase deficiency have the salt-wasting form. Because of low levels of aldosterone, sodium resorption in the renal tubules is reduced, resulting in hyponatremia and hyperkalemia. If this salt-wasting condition goes undiagnosed and unmanaged, shock and death may result in the first few weeks after birth. Newborn screening programs are currently in place in all 50 US states. These programs screen for elevated 17α-hydroxyprogesterone, targeting identification of patients with 21-α-hydroxylase deficiency, and are less sensitive for detection of neonates with 11-β-hydroxylase deficiency and 3-β-hydroxysteroid dehydrogenase deficiency.

The 46,XY DSD is secondary to insufficient testosterone production or insensitivity at the cellular level. Androgen insensitivity, the most common cause of this disorder, is the result of an abnormality or a reduction in the number of androgen receptors. Not all affected individuals present with ambiguous genitalia at birth because the spectrum of sensitivity is broad. If the androgen receptor is completely nonfunctional or absent, the external genitalia are those of a normal female (ie, complete androgen insensitivity syndrome). In

the setting of partial function of the androgen receptor, genital ambiguity occurs. This is an X-linked condition that affects only 46,XY individuals; however, 46,XX females are carriers and pass the mutation to their offspring.

Other causes of 46,XY DSD are inadequate testosterone production secondary to low levels of fetal gonadotropins; defects in testosterone synthesis from enzyme deficiencies or disruption of electron transport; failure to convert testosterone to DHT as a result of 5-α-reductase deficiency; deficient müllerian duct-inhibiting substance, which can be autosomal recessive or X-linked recessive; and intrauterine loss of both testes secondary to torsion or another prenatal event. Causes of testosterone deficiency resulting in 46,XY DSD include CAH caused by defects of StAR, P-450 side-chain cleavage, 3-β-hydroxysteroid dehydrogenase, 17-α-hydroxylase, and P-450 oxidoreductase.

Although SRY is considered to be the sex-determining region, defects in SRY explain only approximately 15% of XY gonadal dysgenesis. A loss of function mutation in *SOX9* results in camptomelic dysplasia with XY sex reversal. More recently, an abnormality of a gonad-specific regulatory region of *SOX9* resulted in isolated XY gonadal dysgenesis. Steroidogenic factor 1 mutations have been estimated to account for up to 13% of cases of XY gonadal dysgenesis.

Although most causes of ambiguous genitalia are related to chromosomal abnormalities and inherited enzymatic defects, exogenous sources of hormones can affect the differentiation of sexual organs. In most cases, the effect is minimal and no ambiguity occurs. Masculinized female external genitalia can occur, however, depending on the timing and duration of prenatal exposure to androgens or other virilizing drugs. Currently, the most commonly used androgens are likely anabolic steroids. A neonate may even be exposed prenatally through transdermal passage to the mother from a family member using androgen creams. An adrenal tumor or poorly controlled CAH in the mother will also result in virilization of the female fetus. The progestin in birth control pills does not have sufficient androgen action to cause a problem.

Differential Diagnosis

The differential diagnosis of ambiguous genitalia depends on the classification of the DSD (Table 107.1). Some causes of this condition can be life-threatening and must be recognized immediately (eg, salt-wasting CAH).

Evaluation

History

The general obstetric history should be reviewed, although it may not be helpful in all cases. Likely the most important source of information on family history can be derived from family pedigrees (Box 107.2). The mother of the affected newborn should be interviewed thoroughly for any clinical findings that might suggest her as the source of androgens. Undiagnosed chromosomal disorders, consanguinity, and recurrent medical conditions may be established or inferred from the family background.

Table 107.1. Classification and Causes of Disorders of Sexual Differentiation in the Newborn

Disorder	*Causes*
46,XX DSD	Congenital adrenal hyperplasia
	Maternal androgen ingestion
	Maternal virilizing hormones
	Idiopathic (associated with dysmorphic syndromes)
46,XY DSD	Biochemical defects in testosterone biosynthesis (eg, enzyme deficiencies)
	Androgen insensitivity (eg, complete or partial receptor defects)
	5-α-reductase deficiency
	Persistent müllerian duct syndrome
	Gonadotropic failure
	Dysgenetic testes
	Bilateral vanishing testes syndrome
	Idiopathic (associated with dysmorphic syndromes)
Ovotesticular DSD	Chimerism
46,XX testicular DSD or 46,XY complete gonadal dysgenesis	Chromosomal mosaicism

Abbreviation: DSD, disorders of sexual differentiation.

Box 107.2. What to Ask

Ambiguous Genitalia

- Did the mother take any medications containing estrogen, progestational agents, or androgens during the pregnancy? Did she use any other virilizing drugs, such as danazol, during pregnancy?
- Was the mother in contact with anyone using hormonal creams or gels?
- Does the mother have poorly controlled congenital adrenal hyperplasia or an adrenal tumor? Does the mother have any virilizing symptoms that suggest she should undergo an evaluation for these conditions?
- What is the mother's prior obstetric history?
- Did she have any problems with any previous pregnancies?
- Does a history exist of any unexplained neonatal deaths, particularly in male offspring?
- Are her other children growing and developing normally?
- Does a family history exist of ambiguous genitalia, including microphallus, hypospadias, and cryptorchidism?
- Does a family history exist of sterility, female hirsutism, or amenorrhea?
- Are the parents or other family members consanguineous?

Physical Examination

A complete physical examination of the newborn must be performed in the nursery, in addition to a detailed assessment of genitalia. In particular, the presence of dysmorphic features (eg, microcephaly, low-set ears, micrognathia) that are suggestive of a chromosomal abnormality should be appreciated. The areola should be examined for any evidence of hyperpigmentation, and the inguinal area should be palpated for any masses or hernias.

A thorough genital examination should be performed. The appearance and size of the labioscrotal folds should be noted in terms of pigmentation, presence of rugae, and size. The physician should keep in mind that normal female labia majora may not completely cover the labia minora and that the labia may be extremely underdeveloped in the preterm newborn. The physician should determine whether any masses are palpable in what appear to be the labia and whether the testes are palpable in what appears to be the scrotum. The size of the phallus/clitoris should be measured; in term neonates, a normal stretched phallus is at least 2.5 cm long, whereas a normal clitoris should not exceed 1 cm. The labioscrotal folds should be spread apart to look for a vaginal introitus. The presence of posterior labioscrotal fusion, which may preclude this, confirms the suspicion of indeterminate genitalia. The *clitoral index*, that is, the product of the clitoral transverse and sagittal dimensions, and the anogenital distance can be determined by an experienced physician. Limited data on these measurements in normal children are available in the literature. The location of a urethral meatus should be noted, because if hypospadias and cryptorchidism occur together, the chance of DSD is approximately 50%. A rectal examination may help detect the presence of a uterus or prostate but may be difficult to perform.

Laboratory Tests

The most important laboratory study to obtain is a karyotype, which can be performed in 24 to 48 hours by many laboratories. Examination of Barr bodies in a buccal smear is not recommended because this test is unreliable. Additionally, a serum electrolyte panel should be ordered in the nursery and electrolyte levels monitored closely if CAH is suspected. A serum 17-α-hydroxyprogesterone level is mandatory in evaluation for CAH. Other intermediate metabolites, such as 11-deoxycortisol, androstenedione, dehydroepiandrosterone-sulfate, and sex steroids (ie, testosterone, DHT) also can be measured to evaluate for androgen excess or deficiency. Measurement of 17-ketosteroids and pregnanetriol in the urine may provide supportive data in the neonate with ambiguous genitalia, especially in one in whom the gonads are not palpable.

A human chorionic gonadotropin stimulation test may be performed to measure response in testosterone production if ovotesticular DSD is suspected.

Imaging Studies

Pelvic ultrasonography is effective in determining if müllerian structures are present, but this technique is not as useful for locating the gonads. If the gonads are not palpable, magnetic resonance imaging of the pelvis may be considered. Genitography can aid in visualizing the duct structures under fluoroscopy.

Management

An interdisciplinary team consisting of a pediatrician, pediatric endocrinologist, medical geneticist, urologist, social worker, and psychologist or psychiatrist should be involved in the care of the newborn with DSD with ambiguous genitalia. With such management, all aspects of care can be addressed in an efficient and comprehensive manner. A consensus statement on management of infants with DSD was published in 2006 and proposed ethical guidelines for management were published in 2010.

Initial Phase: Delivery Room and Newborn Nursery

If the sex of the newborn is uncertain, it should not be assigned in the delivery room. The parent or parents and nursing staff should be notified immediately of the ambiguity, and a unisex name should be assigned, such as "Baby Smith" rather than "Baby Boy Smith" or "Baby Girl Smith." Hospital nameplates should also reflect a sex-neutral status in wording and color. The physician should congratulate the parent or parents on the birth of the child, then inform them of the genital ambiguity. The physician should advise the parent or parents that additional tests are necessary to determine the baby's sex. The parent or parents should be encouraged not to speculate on the sex of the newborn in the meantime.

During the initial hours after birth, parents may have difficulty comprehending the condition. An open line of communication must be maintained with the family, even while waiting for test results. Parents should be assured that sex assignment will be made as soon as possible and that more information will follow with test results. Sex assignment can potentially be made within 3 to 5 days or even earlier in some institutions because most preliminary laboratory results are reported in 24 to 48 hours. However, some cases may require more extensive workup, such as a trial of testosterone in partial androgen insensitivity, so sex assignment for these neonates may take more time. The interval of time to sex assignment, therefore, must be individualized. Necessary radiographic studies should be ordered as soon as possible.

Intermediate Phase: Psychological Issues

Several psychological issues should be addressed at the time of diagnosis. Alleviation of parental anxiety about the cause of the condition should be the priority; general questions can be answered as well. For example, a parent may be unclear about what to tell others about the sex of the newborn and may find this process quite awkward. Additionally, the parent or parents should be educated about normal sexual differentiation. The pediatrician must emphasize that during the first 6 to 8 weeks of gestation, sexual organs are undifferentiated. Ambiguous genitalia should be explained as overdevelopment or underdevelopment. For parental perspective, genital ambiguity can be compared with another type of birth defect, such as a cardiac septal defect.

The primary care physician must also assess the level of sophistication of the parent or parents as well as their cultural and/or religious beliefs about gender identity and sexual orientation. The sex preference for the newborn should be addressed. The physician should ask whether a boy or girl was hoped for and whether strong parental feeling existed about a particular sex. The medical team can also help the family establish a plan for the newborn concerning what to share with the extended family and how much detail they want to disclose. After the initial meeting and while awaiting laboratory data, other questions about sexual orientation, puberty, fertility, and self-esteem may arise.

Final Phase: Sex Assignment

After the karyotype is confirmed and the type of DSD has been considered, team members should meet with the family to discuss sex assignment before discharge from the hospital. Traditionally, sex assignment was based on size of the phallus, potential response to androgen stimulation, and potential for fertility. More recently, additional factors have been recognized as important in sex assignment, including in utero brain exposure to androgens and likely adult gender identity, quality of sexual function with or without surgery, and psychosocial risk for patient and family in the event of gender dysphoria. The parent or parents must be involved in this decision and must understand the potential outcome. Some investigators strongly believe that sex reassignment and genital surgery should be discussed with the patient at a later date and that assignment during the neonatal period be avoided. Such an approach involves consistent counseling for the patient, open discussion among the family, and involvement of a primary care physician who is willing to work diligently with the patient and family. Support groups should also be offered regardless of the decision about sex assignment.

The physician should reiterate the detailed information about the origin of the condition. The timing and nature of any future hormonal treatment and surgical procedures should be addressed as well. The parent or parent should be urged to move beyond the issue of ambiguous genitalia after a decision about sex has been made. After that, the parent or parents must make decisions about activities such as birth announcements and inquiries about the neonate's sex from extended family, siblings, and babysitters. The entire medical team should offer the parent or parents encouragement concerning their parenting ability.

Additional Management

Hormone replacement therapy is indicated for some newborns with ambiguous genitalia. Cortisol replacement is mandatory in the newborn with CAH at daily physiologic doses of 10 to 20 mg/m^2. In the newborn with salt-wasting or classic 21-α-hydroxylase deficiency, mineralocorticoid replacement is indicated. Oral fludrocortisone should be administered at doses that suppress plasma renin activity to normal levels without causing hypertension.

Testosterone or estrogen replacement is necessary at puberty for the patient with a disorder in which the gonads did not develop or were surgically removed. For disorders involving micropenis, injections of testosterone cypionate at regular intervals may be used to increase the length and width of the phallus. Recombinant human growth hormone replacement may also be considered for short stature in the patient with mixed gonadal dysgenesis.

Surgical procedures may be necessary in many cases but can be done later in infancy. In the patient with partial androgen insensitivity, surgery may be deferred until later in life because of the high rate of gender dysphoria known to occur among these patients. Although laparoscopy or laparotomy may be indicated for a gonadal biopsy, this is generally not needed in the neonatal period for sex assignment. A gonadectomy is indicated prophylactically in all phenotypic females with all or part of a Y chromosome because of the potential for malignant conversion of gonadoblastoma. Clitoral reduction and recession, vaginoplasty, and labioscrotal reduction are usually performed if the newborn is to be raised female. For the newborn to be raised male, orchiopexy, hypospadias repair, and chordee release often are indicated, but these surgical procedures may be difficult. In some specific cases, however, surgery should be delayed until response to medical treatment is evaluated. For example, in CAH, clitoral size may decrease with glucocorticoid replacement.

Psychological support for the patient and family will be necessary during the child's growth and development into adulthood. Issues of gender identity, gender role, and sexual orientation require ongoing discussion with the patient and parent or guardian. Gender dissatisfaction may occur later in life.

Prognosis

The prognosis for most newborns with ambiguous genitalia is excellent. Problems arise with undiagnosed CAH, which may result in shock and death in the neonatal period if unrecognized and untreated. Otherwise, children should be able to live long, healthy lives after their families have accepted the diagnosis. Amenorrhea in females and sterility in males or females must be addressed during adolescence, at which time psychological services should be provided.

CASE RESOLUTION

The newborn has ambiguous genitalia. The parents should be informed immediately of this finding, and all references related to sex should be avoided. A karyotype and 17-α-hydroxyprogesterone analyses should be performed immediately. Additionally, serial serum electrolyte panels should be performed starting at 12 to 24 hours after birth. The physician should meet with the family to further discuss DSDs and explain the diagnostic workup. General psychological services and information about support groups should be provided as well.

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CHAPTER 108

Inguinal Lumps and Bumps

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CASE STUDY

A 2-month-old boy presents to your office for evaluation of a lump that has been evident in his right groin for the past week. The lump has been coming and going, and his mother notices that it is larger when he cries. Today, the lump is prominent, and the infant seems fussy. He has been crying more often than usual and vomited once today. His history is remarkable for having been born at 32 weeks of gestation by spontaneous vaginal delivery. Birth weight was 1,500 g (3.3 lb), and he did well in the nursery, with no respiratory complications. He was sent home at 4 weeks of age and has had no other medical problems. He breastfeeds well and has normal stools.

Physical examination reveals a well-nourished, irritable infant in no acute distress. His vital signs demonstrate mild tachycardia and a temperature of 37.8°C (100°F). His abdomen is soft, and the genitourinary examination is significant for a swelling in the right inguinal area that extends into his scrotum. The mass is mildly tender and cannot be reduced. The remainder of the examination is normal.

Questions

1. What are the possible causes of an inguinal mass?
2. How does age affect the diagnostic possibilities?
3. How does the physician differentiate between acute and nonacute conditions?
4. What diagnostic modalities can help with the diagnosis?
5. What are the treatment options for inguinal masses?
6. What, if any, are the long-term consequences of inguinal masses?

Inguinal masses arise from disease in normal tissue in the inguinal area or from ectopic tissue, frequently of embryologic origin. A child may present with the chief report of an inguinal mass, and the mass may be located anywhere along the inguinal canal to the scrotum or labia (Figure 108.1). Along the inguinal canal, a mass might be an enlarged lymph node, a retractile testis, an ovary, or a synovial cyst. At the inguinal ring, a mass might also be a testis or an ovary, or an inguinal hernia. In the scrotum, swelling can result from hernia, hydrocele, varicocele, trauma, or testicular pathology. The labial lesion can be secondary to trauma; an ectopic ovary; mixed gonadal tissue; an actual testis, as in testicular feminization; or a Bartholin cyst. The differential diagnosis and subsequent evaluation vary based on the location of the mass, patient age, and the acuity of presentation of the mass.

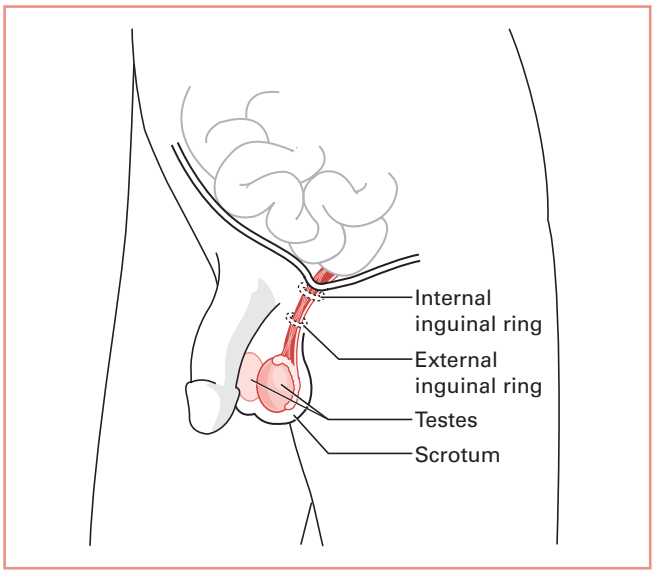

Figure 108.1. The inguinal area of a male individual.

Epidemiology

Inguinal masses are a fairly frequent finding reported in the office setting. The usual cause is an enlarged lymph node, but hernias and hydroceles are also common. The most common surgical procedures performed in children are to repair hernias and hydroceles. The prevalence of inguinal hernias has been estimated to be 1 to 4 per 100 live births. There is a 60% risk of incarceration in the first 6 months after birth if the hernia is left untreated. For this reason, surgical correction is recommended early. Hernias are present on the right side in 60% of cases, are present on the left side in 30%, and are bilateral in 10%. Of affected children, males outnumber females 4:1. Femoral and direct hernias are more common in girls. Certain conditions are associated with an increased incidence of hernias (Box 108.1). The most significant predisposing factor is preterm birth, with hernias reported in 30% of newborns weighing less than 1,000 g (<2.2 lb) at birth.

For the other common acute scrotal lesions, 1 out of 160 males experience either testicular torsion or torsion of the appendix testis. Testicular torsion may occur in utero, but the peak

Box 108.1. Conditions Associated With Increased Risk for Hernia in the Neonate

- Abdominal wall defect
- Ascites
- Connective tissue disease
- Cystic fibrosis
- Family history
- Low birth weight
- Mucopolysaccharidosis
- Preterm birth
- Undescended testis
- Urologic malformations

incidence of testicular torsion occurs in the perinatal period and again at puberty. Torsion of the appendix testis is most likely to occur between ages 7 and 10 years. Varicoceles occur in pubertal and postpubertal males, with a fairly high rate of up to 15%. Testicular tumors are rare in childhood, occurring in 0.5 to 2.0 per 100,000 children and accounting for only 1% of all pediatric solid tumors. In adolescence, however, testicular cancer is the most common cause of cancer in young males and may affect as many as 1 in 10,000.

Clinical Presentation

The child with an inguinal mass presents acutely or nonacutely. In the acute presentation, the swelling occurs rapidly and is associated with pain. The associated systemic symptoms of nausea and vomiting may occur. Inguinal pathology should be suspected in any child with abdominal pain. The involved area may be extremely tender. Nonacute masses appear more slowly. Some may be present from birth. They may come and go, especially with crying or straining. Nonacute masses usually are not tender and are not associated with systemic symptoms (Box 108.2).

Box 108.2. Diagnosis of Inguinal Masses

Acute

- Rapid onset
- Painful
- Tender
- Nausea and vomiting
- Fever
- Overlying skin red
- Cremasteric reflex absent

Nonacute

- Slower onset
- Not painful
- May fluctuate in size
- Cremasteric reflex present

Pathophysiology

Pathophysiological developmental features of an inguinal mass vary depending on the cause of the mass. An enlarged lymph node may result from proliferation of intrinsic lymphocytes or inflammatory infiltrate from infection (eg, lymphadenitis). The etiology of lymphadenopathy is extensive (see Chapter 100). Any of these processes can occur in the inguinal nodes. An enlarged node also can be secondary to metastatic infiltration from another cell line and can represent tumor spread.

A hydrocele develops secondary to failure of obliteration of the patent processus vaginalis during embryologic development. During the 27th to 28th weeks of gestation, the testicle, gubernaculum, and processus vaginalis descend from the peritoneum through the inguinal canal into the scrotum. The processus vaginalis begins closing before birth and attaches to the testis, forming the tunica vaginalis testis. The closure is complete by 1 to 2 years of age. Failure of closure results in a hydrocele if the processus vaginalis fills with fluid and results in a hernia if intra-abdominal contents intermittently descend through the processus vaginalis. Either of these may bulge into the inguinal canal and scrotum. The *incarcerated hernia* is one that cannot be reduced and that places abdominal contents at risk for vascular compromise. This condition is a surgical emergency.

Sometimes a parent or guardian may misinterpret a normal testicle in the process of descent as an abnormal mass. A delay in the normal descent process of the testis occurs occasionally, and the testicle may not be in the scrotum at the time of birth. Torsion of the testis after it has reached the scrotum can occur in the newborn if the testis twists on the spermatic cord. Similarly, the testicle also can twist in the pubertal period on its own vasculature within the tunica vaginalis. This frequently occurs secondary to a high attachment of the tunica vaginalis to the spermatic cord, allowing the testis to hang freely, like a bell clapper. Both types of torsion cause vasculature compromise and an ischemic testis, and both types are surgical emergencies.

Likewise, a vestigial remnant called the "appendix testis" can twist, resulting in vascular compromise of that localized part of the testis.

Pathologically, a traumatic scrotal mass is usually a hematoma, although testicular rupture may occur if the tunica albuginea of testis is torn as a result of trauma. Testicular neoplasms in prepubertal children tend to be germ cell tumors. Yolk sac tumors, teratomas, and mixed germ cell tumors with infiltration of their respective cell lines are the usual diseases found.

A varicocele, another scrotal mass, is caused by increased pressure within the venous drainage of the testicle with subsequent dilatation of the veins, producing a mass. Because of the anatomy of the venous drainage, 90% of varicoceles occur on the left side.

Infections of the epididymis or testis can cause an inflammatory infiltrate and swelling. In female individuals, infection of the Bartholin gland in the labia creates an abscess and results in an acute, painful mass.

Differential Diagnosis

Location, acuity, and patient age aid in establishing the differential diagnosis. Nonacute masses, which have a slow onset and are not painful, include lymphadenopathy, a retractile testis, hydrocele, hernia, varicocele, tumor, and ectopic ovary. Acute masses that have a sudden onset and are associated with pain include epididymitis, orchitis, testicular torsion, traumatic hematoma, torsion of the appendix testis, lymphadenitis, and incarcerated hernia (Box 108.3).

Skin changes can mimic an acute scrotal mass. Henoch-Schönlein purpura, a vasculitis of unclear etiology, can manifest in the scrotal area. Scrotal edema can also occur acutely.

Testicular torsion occurs most commonly in the newborn period and again at puberty. Incarcerated hernias occur most often in the first 6 months after birth. Varicoceles are almost always noted in adolescence and are located in the upper left area of the scrotum. Testicular tumors occur most commonly in adolescence.

The sex of the patient influences the differential diagnosis of the lesion as well as the workup.

Evaluation

History

A thorough, focused history helps define the differential diagnosis (Box 108.4). Inquiring about systemic symptoms should always be included and, if present, may be suggestive of a more generalized process, such as a tumor or systemic infection. Symptoms of dysuria are suggestive of epididymitis or orchitis. A history of trauma or possible sexual abuse should always be sought. The patient with hernia or testicular torsion may have a positive family history for the same condition.

Box 108.3. Differential Diagnosis of Inguinal Masses

Nonacute

- Ectopic ovary
- Hernia
- Hydrocele
- Lymphadenopathy
- Retractile testis
- Synovial cyst
- Testicular tumor
- Varicocele
- Venous aneurysm

Acute

- Bartholin abscess
- Epididymitis
- Henoch-Schönlein purpura
- Idiopathic scrotal swelling
- Incarcerated hernia
- Lymphadenitis
- Orchitis
- Testicular torsion
- Torsion of appendix testis
- Trauma

Box 108.4. What to Ask

Inguinal Masses

- How long has the mass been present?
- Is it painful?
- Does it come and go?
- Was there a history of trauma?
- Does the child have dysuria?
- Does the child have fever or vomiting?
- Does the child have any other masses?
- Has the child had any lower extremity infections?
- Does a history exist of renal disease?
- Does a history exist of preterm delivery?
- Does a positive family history exist for the condition?

Physical Examination

A complete physical examination should be performed. Evidence of diffuse adenopathy may be present. With an inguinal mass, a concentrated, thorough examination of the inguinal area and lower extremity is necessary. A lower extremity lesion may be indicative of a reactive adenopathy. If the mass is not apparent on inspection and it comes and goes, the physician should ask the parent or guardian to point to the location of the mass. The skin is observed for evidence of erythema, swelling, or bruising. The inguinal canal is gently palpated for a mass, after which the scrotal or labial area is assessed. If the mass is of acute onset, the physician should observe the scrotum (in the male patient) and attempt to localize the tenderness. Incarcerated hernia, testicular torsion, torsion of the appendix testis, epididymitis, and orchitis are extremely tender. Torsion of the appendix testis may present with the classic blue dot at the upper pole of the testis. The physician should attempt to elicit a cremasteric reflex. The presence of this finding is strongly diagnostic for a condition other than testicular torsion. The testis with a horizontal lie may be indicative of a bell clapper deformity. The pain of epididymitis and orchitis is partially relieved when the testis is elevated (ie, Prehn sign). Transillumination of the mass may be helpful. A fluid-filled mass, such as a hydrocele, will definitely transilluminate; incarcerated bowel may transilluminate as well.

Accurate measurement of the mass is necessary. Evaluating the borders of an inguinal mass is important. A hydrocele does not extend into the inguinal canal; therefore, the top border can be felt below the pubis. A hernia will extend into the inguinal canal, so an upper border will not be apparent. Use of gentle pressure to reduce the hernia should be attempted. A hernia that is not readily apparent may be demonstrable by causing the infant to cry and thereby increasing intra-abdominal pressure. The older child should be asked to stand and cough while the inguinal canal is palpated. A varicocele, which feels like a bag of worms, is a nontender mass over the

spermatic cord and is readily palpated if the adolescent patient is in a standing position.

Laboratory Tests

Laboratory tests should be directed toward the most likely diagnosis as determined by the history and physical examination. If an infection is suspected, a complete blood cell count should be obtained. If the infection is thought to be epididymitis or orchitis, a urinalysis and urine culture, along with tests for gonorrhea and chlamydia, should also be obtained. If lymphadenopathy is suspected, a complete blood cell count, mononucleosis test, cat-scratch disease test, and possibly a biopsy may be necessary. An inguinal mass in a female may be a normal testes, and chromosomal evaluation may be indicated to diagnose a disorder of sexual differentiation (see Chapter 107). If a tumor is suspected, the α-fetoprotein level, which is elevated in 90% of patients with yolk sac tumors, and β-human chorionic gonadotropin should be assayed.

Imaging Studies

Ultrasonography can be helpful in defining inguinal masses and is the best test to define scrotal contents. It can be useful in differentiating between enlarged lymph nodes, in which a characteristic central echolucent area can be seen, and hydrocele or hernia. Ultrasonography provides accurate information for evaluating tumors. It is the imaging test of choice and can aid in identifying a mass as ovarian or testicular because the ovary is smaller and more echogenic and may have follicular cysts. Color Doppler ultrasonography is the most accurate test for evaluating the scrotum of the patient with acute symptoms to identify a testicular fracture and to assess blood flow in the patient with testicular torsion; however, because of the time required for the test, its use may not be practical in the acute setting. Nuclear imaging may be possible, but the time required for the study may be prohibitive. In the patient with suspected incarcerated hernia, a plain radiograph of the abdomen is helpful to detect signs of intestinal obstruction. Computed tomography and magnetic resonance imaging are only moderately effective in this setting and generally are not recommended.

Management

Many inguinal masses require surgical treatment. Acute symptoms involving the scrotum present a surgical emergency, and it may not be possible to conduct diagnostic studies because of time constraints. If a high probability exists for testicular torsion, immediate surgical exploration of the scrotum is warranted. Surgery within 4 to 8 hours of symptom onset has an excellent rate of a viable testis. The possibility of a viable testis becomes progressively worse if surgery is performed more than 8 hours after symptom onset. After 48 hours, it is unlikely that the testis can be salvaged. If the testis is nonviable, it is removed. It is not necessary to perform surgical exploration for torsion of the appendix testis if the diagnosis is certain.

Surgical intervention may also be indicated in the setting of scrotal trauma, which can cause torsion or testicular rupture. A urologic referral is indicated for assessment.

All hernias require surgical repair at some time. Immediate surgery is indicated for an incarcerated hernia that cannot be reduced. For the hernia that can be reduced, however, elective surgical repair can be scheduled. Controversy exists about the indications for surgery on the contralateral side. An infant younger than 1 year has a 20% chance of developing a hernia on the other side, and most surgeons repair both sides at the same time. Other accepted indications for exploration of the unaffected side include preterm status, twin gestation, left-sided hernia, increased abdominal pressure, and female sex. Currently, some surgeons use laparoscopy at the time of the hernia repair to define a patent processus vaginalis on the opposite side and repair it if patency is found. It is not necessary to repair a hydrocele surgically unless it persists beyond 1 year of age. Because this persistence implies a peritoneal connection and an impending hernia, repair is indicated. Testicular fracture also necessitates surgical repair. Varicoceles are removed if pain is significant, the testicle shows growth retardation, bilateral disease is evident, or the teenager has a solitary testis. Currently, it is possible to perform subinguinal microsurgical varicocelectomy to preserve lymphatic drainage. All testicular tumors are removed. Use of additional antitumor therapy is dependent on the stage and cell line of the tumor.

Infectious inguinal masses are treated according to the specific bacteriologic diagnosis using antibiotics, and incision and drainage as indicated.

Prognosis

After surgical treatment of an inguinal hernia or testicular torsion, the child generally does well. The most significant long-term complication of hernia surgery is subsequent impaired testicular function; additionally, decreased testicular size is noted in up to 27% of cases. Damage to the vas deferens and testicular vessels may impair spermatogenesis and result in an increased incidence of impaired fertility. Surgery for testicular torsion may also be associated with subsequent infertility, particularly if an affected testis is left in place. Two-thirds of affected testicles demonstrate atrophy. For the patient who experiences loss of a testis, the physician should offer a prosthesis in the future because of the potential for significant psychological implications.

The risk of recurrence of a hernia after repair is low. Increased abdominal pressure and history of incarcerated hernia predispose to recurrence, with a rate of up to 12% in children with ventriculoperitoneal shunts. A hydrocele may manifest after varicocele repair.

CASE RESOLUTION

The infant's history of prematurity associated with a mass that comes and goes most likely indicates an inguinal hernia. Based on the additional symptoms of pain, fever, and vomiting and the findings of an inflamed, nonreducible mass on physical examination, a high likelihood exists for the diagnosis of incarcerated hernia. The infant is taken to the operating room, where this diagnosis is confirmed. The hernia is reduced and repaired, and the intestine is noted to be viable. The contralateral side is explored and found to be normal. The infant makes an uneventful recovery.

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CHAPTER 109

Hematuria

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CASE STUDY

A 6-year-old boy is brought to the office for a school entry examination. He was the full-term product of an uncomplicated pregnancy, labor, and delivery. Although he has had 4 or 5 episodes of otitis media, he has generally been in good health. He has never been hospitalized or experienced any significant trauma. He has no known allergies, has been fully immunized, and is developmentally normal. However, his mother states that he has reported occasional mild abdominal pain.

The physical examination is completely normal. Height and weight are at the 75th percentile, and blood pressure is 100/64 mm Hg. Screening tests for hearing and vision are normal. Hematocrit is 42. The urinalysis comes back with a specific gravity of 1.025, pH 6, 2+ blood, and trace protein. Microscopic examination shows 18 to 20 red blood cells per high-power field; 0 to 1 white blood cells per high-power field; and a rare, fine, granular cast.

Questions

1. What disease entities cause hematuria?
2. How should hematuria be evaluated?
3. How does the approach to hematuria differ in children who report dark or red urine?
4. What is the appropriate follow-up of children with asymptomatic microscopic hematuria?

Hematuria is a common problem in pediatric patients, and primary care physicians should have a clear understanding of its pathophysiology, etiology, evaluation, and therapy. Hematuria can be caused by a serious medical problem, or it may be only an incidental finding with no potential for impairment of patient health. Generally, hematuria is categorized as gross or microscopic. The etiology of and approach to hematuria vary based on the severity and symptomatology. *Gross hematuria* is defined as red or brown urine caused by the presence of red blood cells (RBCs). Microscopic hematuria is defined as 3 or more consecutive urine samples with a positive dipstick and 6 or more RBCs per high-power field in a fresh, spun urine sample.

Epidemiology

The prevalence of gross hematuria is approximately 1.3 in 1,000 patient visits (Table 109.1). In 1 series, the causes in approximately one-half of the patients were readily apparent from the intake history or physical examination. The incidence of gross hematuria may increase in the community during an epidemic of a disease, such as acute glomerulonephritis, a condition often associated with gross hematuria. In another series, approximately 30% of children with gross hematuria had glomerular diseases, most commonly immunoglobulin (Ig) A nephropathy. The incidence of kidney stones, another cause of hematuria, is increasing in the pediatric population.

Microscopic hematuria is a more common problem among pediatric patients. Prevalence rates for persistent microscopic hematuria range from 0.5% to 2.0%, but 4% to 5% of school-age children may have microscopic hematuria on a single voided specimen. The incidence is artificially increased in the summer because at that time children tend to visit pediatricians for camp and preparticipation

Table 109.1. Etiology of Gross Hematuria in an Unselected Pediatric Population

Cause	*Patients (%)*
Readily Apparent	
Documented UTI	26
Perineal irritation	11
Meatal stenosis with ulcer	7
Trauma	7
Coagulopathy	3
Stones	2
Total	56
Other	
Suspected UTI	23
Recurrent gross hematuria	5
Acute nephritis	4
Ureteropelvic junction obstruction	1
Cystic cystitis	<1
Epididymitis	<1
Tumor	<1
Unknown	9
Total	44

Abbreviation: UTI, urinary tract infection.

Adapted with permission from Ingelfinger JR, Davis AE, Grupe WE. Frequency and etiology of gross hematuria in a general pediatric setting. *Pediatrics.* 1977;59(4):557–561.

sports physical examinations that typically include a screening urinalysis.

Clinical Presentation

The child with gross hematuria presents with the sudden appearance of red or brown urine, which may be associated with flank or urethral pain or with a history of trauma. It may occur during or within 1 to 2 weeks of a respiratory infection.

The child with microscopic hematuria may have urinary symptoms (eg, dysuria). In the child who appears well, microscopic hematuria is usually detected on screening dipstick examination or on urinalysis obtained for other indications. In 2007 the American Academy of Pediatrics ceased recommending that routine screening urinalysis be done in asymptomatic children and adolescents. Urinalysis often is still requested as part of camp and preparticipation sport evaluations, however. In Japan, because of a high incidence of glomerulonephritis (primarily IgA nephropathy), annual screening urinalysis is performed in schools and seems to have had an effect on early diagnosis and treatment.

Pathophysiology

Gross Hematuria

Gross hematuria occurs because of the presence of large numbers of RBCs in the urine. Blood may enter the urine because of rupture of blood vessels following trauma or inflammation in the glomeruli or interstitial regions of the kidney. It also may occur as a result of severe inflammation of the bladder wall.

Causes of gross hematuria are listed in Box 109.1. The presence of casts in the urine indicates that the red cells are coming from the glomeruli and suggests the diagnosis of glomerulonephritis. The most common causes of glomerulonephritis in children include acute postinfectious glomerulonephritis (most commomly poststreptococcal), anaphylactoid purpura (ie, Henoch-Schönlein purpura), IgA nephropathy, membranoproliferative glomerulonephritis (MPGN), dense deposit disease, and systemic lupus erythematosus (SLE).

Common causes of gross hematuria in the absence of RBC casts include urinary tract infection from bacteria or certain viruses, renal trauma, bleeding diathesis (eg, hemophilia, idiopathic thrombocytopenic purpura), renal tumors, obstruction of the urinary tract, renal stones, hypercalciuria, and hemolytic uremic syndrome (HUS). Hemangioma in the urinary tract is an extremely rare cause of gross hematuria. In endemic areas, gross hematuria may be caused by schistosomiasis. Another rare cause of gross hematuria is nutcracker phenomenon caused by left-sided renal vein congestion from compression of the renal vein by the superior mesenteric artery. The symptoms of nutcracker phenomenon are distinctive: intermittent gross hematuria associated with left-sided flank pain that is relieved by lying down. Another cause is urethrorrhagia, in which children, typically prepubertal boys, pass bloody urine, usually at the end of their voiding and frequently accompanied by spots of blood in the underwear.

Box 109.1. Common Causes of Gross Hematuria in Pediatric Patients

Glomerular Causes
- IgA nephropathy
- Acute postinfectious GN
- Lupus nephritis
- Membranoproliferative GN
- Dense deposit disease
- Anaphylactoid purpura GN
- Alport syndrome
- Thin basement membrane disease
- Rapidly progressive GN
- Vasculitis, ANCA positive
- Anti–glomerular basement membrane disease
- Hemolytic uremic syndrome

Hematologic Causes
- Sickle cell disease or trait or hemoglobin C
- Hemophilia
- Thrombocytopenia
- Thrombosis (renal arterial or venous)

Structural Causes
- Renal trauma
- Tumor
- Obstruction
- Renal stones
- Polycystic kidney disease
- Foreign bodies

Vascular Abnormalities
- Hemangiomas
- Nutcracker phenomenon
- Arteriovenous malformations

Infectious Causes
- Bacterial urinary tract infection
- Viral cystitis
- Schistosomiasis
- Tuberculosis

Interstitial Diseases
- Acute interstitial nephritis
- Tubulointerstitial nephritis with uveitis

Other
- Hypercalciuria
- Munchausen by proxy
- Urethrorrhagia

Abbreviations: ANCA, antineutrophil cytoplasmic autoantibody; GN, glomerulonephritis; IgA, immunoglobulin A.

Microscopic Hematuria

Microscopic hematuria occurs when small numbers of RBCs enter the urine via tiny ruptures in the glomerular capillary walls or in the capillaries of the tubulointerstitium or bladder lining. One study

showed that otherwise healthy children with microscopic hematuria had increased erythrocyte deformability, making it easier for RBCs to slip through the glomerular capillaries. For purposes of discussion, the following causes of microscopic hematuria are considered: infectious, structural, traumatic, glomerular, and interstitial. Separate consideration of the causes of microscopic and gross hematuria often is helpful, although significant overlap exists. The presence of gross hematuria typically warrants a more rapid, and usually more extensive, evaluation.

Urinary tract infection is among the most common infectious causes of hematuria. Bacterial infections of the bladder or kidney occur much more frequently than viral cystitis. Adenovirus is the most common viral cause of hemorrhagic cystitis and usually is associated with dysuria. Other viral causes include cytomegalovirus, parvovirus 19, and BK polyomavirus nephropathy. Vaginitis in girls and prostatitis in teenage boys also may result in hematuria.

Any type of congenital obstructive uropathy may result in massive dilatation of the urinary tract, which increases the susceptibility for bleeding of the urinary tract, even with trivial trauma. Chronic urinary tract obstruction in children (eg, posterior urethral valves, congenital ureteropelvic junction obstruction) is often asymptomatic. Historically, these conditions typically were diagnosed when children presented with urinary tract infections or gross hematuria after relatively trivial trauma. Currently, congenital urinary tract obstruction typically is diagnosed after a prenatal ultrasonography reveals hydronephrosis in the fetus. Nevertheless, urinary tract obstruction may be detected during an evaluation for asymptomatic microscopic hematuria.

Any tumor of the genitourinary tract may be associated with gross and microscopic hematuria. Pelvic tumors rarely cause urinary obstruction in children, although such tumors frequently cause obstruction in adults. The child with Wilms tumor, the most common childhood renal tumor, usually presents with an abdominal mass but may experience hematuria.

Congenital renal malformations are quite common. Any of these may be associated with hematuria and include polycystic kidney disease, renal dysplasia, medullary sponge kidney, and simple cysts. Patients with polycystic kidney disease may have severe, painful hematuria.

Vascular problems may result in hematuria. Hemangiomas of the kidney, bladder, or ureter are quite rare but may bleed. Arteriovenous malformations also occur infrequently. Hematuria may be a sign of a renal artery or renal vein thrombosis, particularly in sick neonates.

Young children are more susceptible to renal injury, which may result in hematuria, than older children or adults because their kidneys are relatively less protected by the rib cage. Additionally, children may insert foreign objects into the vagina, urethra, and bladder that cause pain and hematuria. Microscopic hematuria has also been described after extremely vigorous exercise, such as marathon running. Child abuse or Munchausen syndrome by proxy should be considered if any suspicions are raised on the basis of the history or physical examination.

Hypercalciuria is another cause of microscopic hematuria. The child with hypercalciuria often has a family history of urinary calculi. Calcium oxalate crystals may be present on microscopic examination of the urine. A urinary calcium-creatinine ratio is best obtained on a first morning, fasting urine sample with reminders to the family that the child should empty the bladder before going to bed. Urinary calcium excretion varies with age. Normal values are listed in Table 109.2.

The 2 types of hypercalciuria are absorptive and renal leak. The child with absorptive hypercalciuria overabsorbs calcium from the gastrointestinal tract, likely because of an exquisite sensitivity to vitamin D, and can be treated with a reduced calcium diet to the recommended daily allowance for age. The child with renal leak hypercalciuria has an inherently higher rate of urinary calcium excretion and may require thiazide diuretics to reduce urinary calcium excretion. Interstitial nephritis, usually resulting from drug exposure, may also cause hematuria. Generally, the patient with interstitial nephritis may exhibit other signs of tubular disease, such as glycosuria, polyuria, or proteinuria.

Glomerular disease may cause gross or microscopic hematuria. Etiologies include acute or chronic glomerulonephritis, such as acute postinfectious glomerulonephritis, MPGN, dense deposit disease, antineutrophil cytoplasmic antibody–associated vasculitis, IgA nephropathy, SLE, thin basement membrane disease or nephropathy, and Alport syndrome. The RBCs originating from glomeruli are dysmorphic, and careful examination of the urine from these patients often reveals RBC casts.

Sickle cell disease, sickle cell trait, and hemoglobin C trait have been associated with gross or microscopic hematuria.

Differential Diagnosis

When a child reports red urine (ie, gross hematuria), the physician must first determine whether it is the result of hematuria or pigmenturia by using a urine dipstick. If the dipstick result is negative for blood, the dark urine is caused by dyes, drugs, or pigments (Table 109.3). If the dipstick is positive for blood, the red color is caused by intact RBCs, hemolyzed RBCs, hemoglobin, or myoglobin;

Table 109.2. Normal Values for Urinary Calcium-Creatinine Ratios[a]

Age	*Urine Calcium-Creatinine Ratio*	*24-Hour Urine Calcium*
Preterm neonate	≤0.82	≤8.9 mg/kg/day[b]
<7 months	≤0.86	
7–18 months	≤0.60	
19 months–6 years	≤0.42	
6 years–adult	≤0.22	<4 mg/kg/day

[a] Samples for calcium-creatinine ratio should be obtained on a fasting, first-voided morning specimen. The calcium and creatinine concentrations must be in the same units (eg, mg/dL) before the ratio is calculated.

[b] For healthy preterm newborns taking no medications. Calcium excretion varies with diet and phosphorus intake, and it is higher if patients are treated with furosemide, xanthines, or glucocorticoids.

Table 109.3. Distinguishing Hematuria From Pigmenturia

Problem	*Urine Color*	*Dipstick*	*Microscopic Appearance*
Hematuria	Red, brown, or red-brown	Positive	Red blood cells
Hemoglobinuria	Red, brown, or red-brown	Positive	Negative
Myoglobinuria	Red, brown, or red-brown	Positive	Negative
Porphyrins	Red	Negative	Negative
Exogenous pigments[a]	Red or orange	Negative	Negative

[a] Some common exogenous pigments include phenytoin, beets, rifampin, nitrofurantoin, sulfas, amitriptyline, methyldopa, phenothiazine, and chloroquine.

the clarification is based on microscopic examination of fresh, spun urine.

The child whose dipstick result is positive for blood but shows no RBCs may have hemoglobinuria or myoglobinuria, or the urine may have been improperly handled en route to the laboratory. Hemoglobinuria may be seen with acute autoimmune hemolytic anemia, drug-induced hemolysis, paroxysmal nocturnal hemoglobinuria, a mismatched blood transfusion, cardiopulmonary bypass, freshwater drowning, and, in some cases, HUS. Myoglobinuria is noted in individuals with rhabdomyolysis. Acute rhabdomyolysis can occur after a crush injury or a very prolonged seizure and in certain susceptible individuals with an inborn error of muscle metabolism. Myoglobinuria also may be occur with the myositis associated with influenza infections. Free hemoglobin and myoglobin are toxic to the renal epithelial cells, mandating generous fluid intake and close monitoring. Serum appears clear in myoglobinuria and pink in hemoglobinuria.

Evaluation

Gross Hematuria

History

The history is crucial to an accurate, efficient, and cost-effective evaluation of patients with hematuria (Box 109.2). The family should be questioned carefully about trauma to the trunk, abdomen, or perineum; recent skin infection or pharyngitis; dysuria; and abdominal or flank pain. The presence of gross hematuria at the onset or the end of urination is associated with bleeding from the urethra or bladder trigone. Parents or guardians should be asked whether the child appears "puffy." A family history of hematuria, kidney disease, hearing loss, SLE, bleeding diathesis, hemolytic anemia, or inborn error of muscle metabolism may be important in the diagnosis.

Box 109.2. What to Ask

Hematuria

- Has the child experienced any recent trauma?
- Has the child had fever or dysuria?
- Does the child have any flank or abdominal pain?
- Does the child have any rashes, joint pains, or edema?
- Does the child have a family history of hematuria, kidney disease, kidney stones, or gross hematuria?
- Is there a family history of bleeding disorders or inborn errors of muscle metabolism?

Physical Examination

A complete physical examination is also essential. Blood pressure should be measured accurately. The skin should be examined thoroughly for rashes or petechiae; the abdomen should be checked carefully for renal masses or tenderness; the genitalia should be examined thoroughly for signs of trauma, masses, or rashes (see Chapter 145); and the joints should be checked carefully for signs of arthritis. Fundi should be examined for any hypertensive changes. Children should be assessed for the presence of edema. Short stature could be a sign of previously undiagnosed chronic renal insufficiency.

A careful cardiac and chest examination is necessary to detect signs of congestive heart failure, a finding sometimes seen in patients with acute glomerulonephritis.

Laboratory Tests

Before obtaining a urine sample, cleaning the genitalia with plain water has been shown to decrease the incidence of false-positive results on urine dipsticks.

Transient microscopic hematuria can be seen in children solely based on the presence of fever and is a benign finding. In children with a pathological basis for their hematuria, careful microscopic examination of a urine sample can help determine whether bleeding originates from the upper or lower urinary tract. Red blood cells originating in the glomerulus have a dysmorphic appearance. The first morning urine sample is the most reliable but is not appropriate in some settings, such as after a motor vehicle crash. Sometimes gross hematuria is so substantial that spinning the urine results in a large pellet of debris that is difficult to examine. In such instances, it is prudent to examine an unspun sample. The presence of RBC casts is indicative of glomerulonephritis; however, the absence of such casts does not rule out this condition.

If the urine shows RBC casts or in the presence of other features that are suspicious for glomerulonephritis, the evaluation should include an antistreptolysin O (ASO) titer, antinuclear antibody (ANA), C3, complete blood cell count and differential with platelet count, blood urea nitrogen and creatinine, serum albumin, and a random urine for a urinary total protein-creatinine ratio. It is important to remember that not all patients with glomerulonephritis exhibit RBC casts.

If the urine shows only large numbers of RBCs, no RBC casts, and no bacteriuria, a complete blood cell count with differential and platelet count, urine culture, and both prothrombin time and partial thromboplastin time should be obtained. A sickle cell test should be considered as well. Hypercalciuria can be evaluated by collecting a first morning sample for calcium-creatinine ratio; a more extensive evaluation to assess risk factors for kidney stones

should include a 24-hour urine analysis that includes assessing urinary calcium, citrate, uric acid, and oxalate.

Imaging Studies

If the urine has large numbers of RBCs, renal ultrasonography should be performed. With gross hematuria and a history of serious trauma, abdominal computed tomography should be performed. Computed tomography without contrast is also an excellent modality to detect kidney stones. A chest radiograph should be obtained of the child with RBC casts to evaluate for evidence of fluid overload. Special renal Doppler ultrasonography studies are indicated if nutcracker phenomenon is being considered in the differential diagnosis.

Microscopic Hematuria

The evaluation of microscopic hematuria is similar to that of gross hematuria. Figure 109.1 outlines an approach to the evaluation of microscopic hematuria.

History and Physical Examination

Because many conditions may cause gross or microscopic hematuria, the same questions for eliciting the history apply to both conditions, and the same careful physical examination is indicated.

Laboratory Tests

Generally, initial evaluation includes a urine culture and a careful microscopic examination of the urine on a fresh sample. If the culture is negative, the hematuria is minimal with no associated proteinuria, and the child is otherwise healthy, the urinalysis should be repeated once or twice over the following 2 weeks. Red blood cell casts always signify a glomerular origin for the RBCs. Casts are best preserved in acidic, concentrated urine. Thus, the first morning urine is the best sample to examine for casts. Red blood cell morphology should be assessed. Red blood cells originating in the glomerulus are dysmorphic and of smaller caliber, whereas those that come from lower downstream have the appearance of normal biconcave disks. Although RBC morphology is best appreciated with the use of a polarizing microscope, with experience, dysmorphic RBCs can be recognized using an ordinary microscope. Red blood cells of glomerular origin have a mean cell volume of 50 μL or less. In contrast, RBCs of nonglomerular origin have a mean cell volume of 80 to 90 μL. The presence of a special form of dysmorphic erythrocyte, the G1 cell, is even more specific for glomerular bleeding. These cells are doughnut shaped and contain 1 or more blebs on their surfaces. However, most urinary microscopic examinations currently are performed by machine, and urine microscopy is becoming a lost art. Many medical schools and residency programs no longer teach students how to perform urine microscopy.

Clotting ability should be determined with a platelet count, prothrombin time, and partial thromboplastin time. A sickle cell test should be performed. Renal function should be screened with a blood urea nitrogen and creatinine, and a urine calcium-creatinine ratio should be determined. A C3, ANA, and ASO titer should also be checked. If a urine dipstick shows more than a trace of protein, a urinary protein-creatinine ratio should also be determined, preferably on a first morning sample. If the family history is positive for renal disease, a hearing screening should be ordered. All immediate family members should have their urine checked for blood.

Analysis of a bloody urine sample with a Coulter counter demonstrates characteristic distribution curves for glomerular and nonglomerular hematuria. This test is not readily available, however.

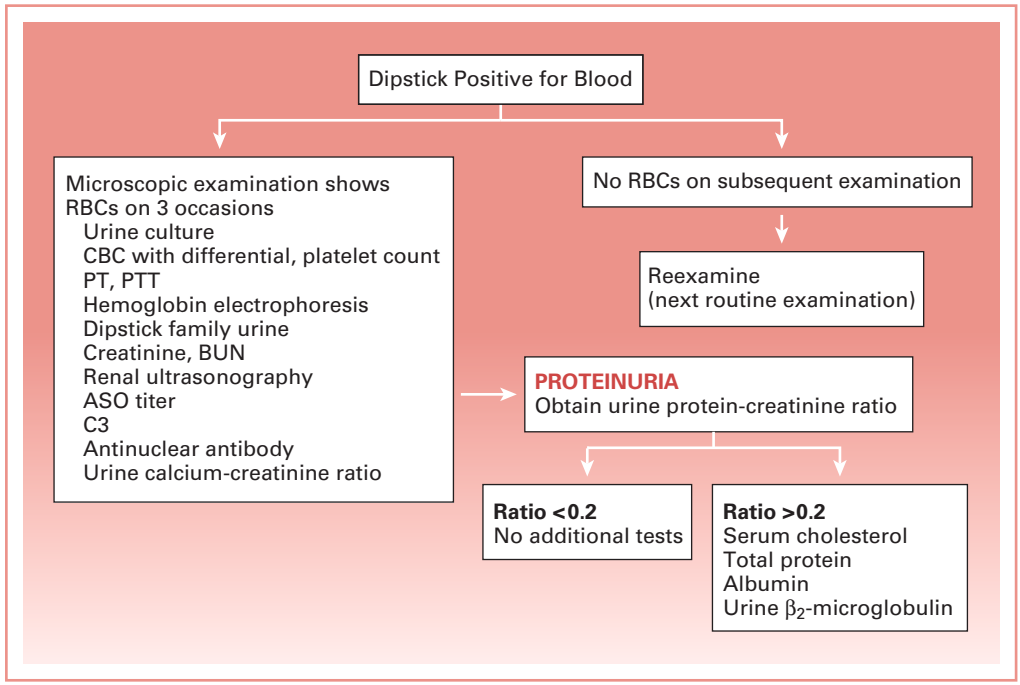

Figure 109.1. Evaluation of asymptomatic, microscopic hematuria.
Abbreviations: ASO, antistreptolysin O; BUN, blood urea nitrogen; CBC, complete blood cell count; PT, prothrombin time; PTT, partial thromboplastin time; RBCs, red blood cells.

Imaging Studies

Renal ultrasonography should be performed to rule out structural abnormalities and tumors. Chest radiographs should be obtained if acute glomerulonephritis is suspected.

Renal Biopsy

The definitive diagnosis of the etiology of hematuria may require a kidney biopsy. Generally, pediatric nephrologists perform kidney biopsies only in select instances after ruling out nonglomerular causes for the hematuria. Indications for renal biopsy in a child with hematuria include an associated abnormal urinary protein excretion, decreased renal function, recurrent macroscopic hematuria, persistently depressed serum complement levels, serologic evidence for SLE, positive antineutrophil cytoplasmic autoantibody (ANCA) testing, hypertension, or a family history suggestive of Alport syndrome or renal insufficiency of unknown etiology.

Glomerular Diseases Associated With Hematuria

Glomerulonephritis

Acute and chronic glomerulonephritis are associated with hematuria. The diagnosis of acute postinfectious glomerulonephritis requires a nephritic urine sediment (ie, RBCs, RBC casts), a low serum complement, and an elevated streptococcal titer (ie, ASO titer, anti-deoxyribonuclease B, positive streptozyme). It is important to document that the serum complement returns to normal within 3 months, because MPGN or dense deposit disease may present in a similar way. The serum complement is chronically depressed in MPGN and dense deposit disease.

The most common form of glomerulonephritis in children is acute poststreptococcal glomerulonephritis. Many patients are asymptomatic, however, and do not come to the attention of physicians. The resulting hematuria may be gross or microscopic. Glomerulonephritis is rarely seen before age 2 years and is most commonly diagnosed in preschool-age and school-age children who typically present with gross hematuria, often with some edema and hypertension. The hypertension may be severe, and occasionally children even have hypertensive seizures. The edema results from transient, acute kidney injury with salt and fluid retention.

Most children with acute poststreptococcal glomerulonephritis experience complete recovery and have an excellent long-term prognosis. Proteinuria is rarely severe enough to cause nephrotic syndrome, and renal failure is rarely serious enough to require dialysis. If hypertension occurs, chest radiography often shows some degree of pulmonary edema, even in the absence of overt clinical signs of congestive heart failure. Any hypertension requires treatment. Other infections cause postinfectious glomerulonephritis, but they are less common and overall less well characterized.

The most common form of chronic glomerulonephritis affecting children is IgA nephropathy. On kidney biopsy, patients have mesangial proliferation with mesangial deposits of IgA as the dominant Ig. In later stages, glomerulosclerosis and interstitial fibrosis are apparent. More than one-third of adults with IgA nephropathy develop end-stage renal disease; the percentage of children who progress to this point is less well known. Gross hematuria in IgA nephropathy is occasionally so severe that patients may pass clots and have flank pain. The presence of persistent proteinuria is considered a poor prognostic sign.

Other forms of primary chronic glomerulonephritis include MPGN, dense deposit disease, mesangial proliferative glomerulonephritis, and membranous nephropathy, which is technically not a form of glomerulonephritis because it usually lacks a significant proliferative component. Children with the previously listed conditions present with hematuria almost always associated with heavy proteinuria.

Secondary forms of glomerulonephritis include lupus nephritis, anaphylactoid purpura, and nephritis associated with various vasculitides, such as Wegener granulomatosis and pauci-immune crescentic glomerulonephritis (eg, ANCA-positive glomerulonephritis). An ANCA panel is indicated in the child with glomerulonephritis and decreased renal function. Children with lupus tend to present with multisystem disease but may have only renal manifestations of the disease. Antinuclear antibody is a good screening test for lupus. If the ANA is positive, C3, C4, and anti-double-stranded DNA should be checked and an antiglobulin (ie, Coombs) test performed.

Anaphylactoid Purpura

Anaphylactoid purpura, also called Henoch-Schönlein purpura, is almost always accompanied by the classic cutaneous vasculitis rash, which is prominent over the lower arms and lower extremities. Abdominal pain may be severe, and affected patients are at risk for developing intussusception. The child with anaphylactoid purpura has microscopic hematuria, which usually clears over time but is occasionally associated with heavy proteinuria and nephrotic syndrome. The child with associated proteinuria is at risk for developing progressive renal disease. All children with anaphylactoid purpura should have their urine monitored for cessation of hematuria or development of proteinuria. The child with heavy proteinuria and suspected anaphylactoid purpura should undergo a diagnostic renal biopsy.

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome is a disease characterized by thrombotic thrombocytopenic purpura, thrombocytopenia, and acute renal failure. Typically, it follows a prodrome of bloody diarrhea resulting from acute colitis caused by a verotoxin-producing strain of *Escherichia coli* (O157:H7), among others, or other enteropathogenic bacteria. The verotoxin is toxic to human endothelial cells. The damaged endothelial cells incite the deposition of fibrin within the glomerular capillaries. These fibrin thrombi result in the shearing of RBCs and consumption of platelets. Several other organisms, such as pneumococcus and *Shigella,* may precipitate HUS. In atypical cases of HUS, the precipitating event may be an upper respiratory infection. Some cases of atypical HUS are familial. The child presents with pallor and severe abdominal pain. Urine output may be diminished as a result of the acute kidney injury, and in many cases dialysis is required. Hypertension may be severe.

Other Glomerular Diseases

Alport syndrome, thin basement membrane disease (ie, benign familial hematuria), focal segmental glomerulosclerosis, and occasionally minimal change disease are also associated with hematuria. Alport syndrome is a disease in which thinning and duplication of the glomerular basement membranes occur. The renal involvement eventually results in end-stage renal disease in males; this outcome is less common in females. Patients or their family members often have nerve deafness or keratoconus. The inheritance of Alport syndrome varies by kindred; it may be autosomal-dominant, autosomal-recessive, or X-linked. The X-linked inheritance is by far the most common mode of inheritance, with female carriers typically being much less severely affected than affected males. Thin basement membrane disease also is characterized by thinning of the glomerular basement membrane; however, the glomeruli are otherwise normal and the clinical course is usually benign. Patients with minimal change disease and focal segmental glomerulosclerosis typically present with nephrotic syndrome but may also have microscopic hematuria.

Management

Gross Hematuria

The management of gross hematuria depends on the underlying cause. The child with a history of trauma should be placed on bed rest pending surgical consultation (see Chapter 76). If the evaluation indicates acute glomerulonephritis and if the child is not hypertensive, careful following as an outpatient is sufficient, with monitoring of blood pressure and renal function with consultation with a pediatric nephrologist. The child with coagulopathy requires treatment specific to the bleeding disorders (eg, intravenous gamma globulin for idiopathic thrombocytopenic purpura). If kidney stones are found, after the acute episode has passed the child should undergo evaluation for stone risk factors.

If some degree of renal insufficiency is present, prompt referral to a pediatric nephrologist is warranted to rule out more unusual causes of glomerulonephritis, for consideration of renal biopsy, and for treatment.

Microscopic Hematuria

Laboratory test results other than urinalysis may be negative in the otherwise healthy child with microscopic hematuria. Some of these children may be recovering from subclinical cases of postinfectious glomerulonephritis, which can cause microscopic hematuria for up to 1 year. Others may have early IgA nephropathy and not yet have significant proteinuria, and some may have thin basement membrane disease or Alport syndrome. As long as a child has normal renal function, normal urinary calcium excretion, normal blood pressure, a negative renal sonogram, no significant proteinuria, and all other tests are normal, it is safe to monitor the asymptomatic child every 3 to 6 months until the problem resolves. The healthy child with an otherwise negative workup who shows no change in clinical state for a period of 1 year may subsequently be monitored annually. If hypercalciuria is detected, a low-calcium diet or treatment with thiazide diuretics may be tried. Increased urinary microalbuminuria has been shown to be predictive of glomerular lesions in children with isolated microscopic hematuria.

Prognosis

The prognosis for the child with hematuria depends on the underlying cause. Compared with microscopic hematuria, gross hematuria is more often associated with serious renal disease, such as acute glomerulonephritis, HUS, or renal trauma. Even so, most children with gross hematuria have a good prognosis, provided the diagnosis is rapidly discovered and appropriate specific therapy is initiated. The child with persistent microscopic hematuria who has no family history of the condition, has a negative evaluation, and does not develop hypertension or proteinuria has an excellent long-term prognosis, although a recent study has shown a small but significantly increased incidence of end-stage kidney disease over 22 years in 16- to 25-year-old individuals with persistent asymptomatic isolated microscopic hematuria.

CASE RESOLUTION

The boy shows no worrisome clinical signs, such as hypertension or significant proteinuria. His urine should be rechecked twice more, and if the hematuria persists, his evaluation should follow the algorithm in Figure 109.1.

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CHAPTER 110

Proteinuria

Elaine S. Kamil, MD

CASE STUDY

A 14-year-old boy is brought to the office for a sports-related preparticipation physical examination. He has been previously healthy but had 1 hospital admission at age 2 years for management of a fractured humerus. He has no acute concerns. The family history is positive for diabetes mellitus in the paternal grandfather and lung cancer in the maternal grandfather. It is negative for renal disease and hypertension. The boy's height and weight are at the 75th percentile for age, and his blood pressure is 110/70 mm Hg.

On physical examination the boy is a well-developed, well-nourished, athletic teenager. No abnormal findings are present. The complete blood cell count reveals a hemoglobin of 14.8 g/dL, a hematocrit of 48.3%, and a white blood cell count of 8,400 cells/mm^3 with a normal differential. The urine has a pH of 5, a specific gravity of 1.025, and 3+ protein on urine dipstick test. The rest of the dipstick test is negative. Microscopic examination shows 0 to 1 white blood cell count per high-power field and 0 to 2 hyaline casts per low-power field.

Questions

1. What conditions cause proteinuria?
2. When should the child with proteinuria undergo further evaluation?
3. What type of evaluation should be carried out to assess proteinuria?
4. When should the child with proteinuria be referred to a pediatric nephrologist?

A small amount of protein is normally present in the urine. In children, normal urine protein excretion is less than 100 mg/m^2 per 24-hour period or 4 mg/m^2 per hour. Urine protein levels increase somewhat under certain conditions, such as vigorous exercise, febrile illness, accidental trauma, and congestive heart failure (CHF). Urinary protein excretion in children is also affected by age, sex, and body habitus. Normally the filtered proteins are of small- to medium-size molecular weights, whereas albumin and other larger molecules mostly are not filtered because of their size. Albumin accounts for less than 30% of the proteins in the urine. Most of the protein in the glomerular filtrate is reabsorbed by the tubular cells. Pathologic amounts of protein are present in the urine when the glomerular leak of protein is increased, when the tubules fail to reabsorb the protein filtered by the glomerulus, or if inflammation in the renal interstitium results in the addition of tubular proteins to the urine.

Urinary protein is initially detected by the urine dipstick; however, this method may produce false-positive results in alkaline or highly concentrated urine. A dipstick test that is positive for protein of 1+ in concentrated urine may not correlate with an abnormal 24-hour urinary protein excretion, whereas a dipstick test result of 1+ in very dilute urine may be associated with an abnormal 24-hour urinary protein excretion. Proteinuria is more accurately determined by performing a timed urine collection or a random sample for chemical determination of the ratio of urinary total protein concentration divided by the urinary creatinine concentration (ie, urine TP/Cr).

Epidemiology

The prevalence of proteinuria depends on how the condition is defined. In a Texas study, 10 mg/dL of proteinuria was found consistently in the urine of 2% to 3% of children in 3 consecutive urine samples. When 50 mg/dL was used as the cutoff for proteinuria, however, only 0.4% to 0.7% of boys and 0.4% to 2.5% of girls had proteinuria in 2 of 3 consecutive samples. The prevalence of proteinuria increased with age. In Finland, approximately 11% of school-age children had at least 1 episode of proteinuria of 25 mg/dL on urine dipstick testing when the urine was tested 4 times. Approximately 2.5% of the children had proteinuria on 2 of 4 occasions.

Clinical Presentation

Proteinuria is a laboratory finding that may present incidentally on a screening urinalysis or be detected during the evaluation of a complaint, such as edema, that may be caused by kidney disease. When proteinuria is detected as an incidental finding in the otherwise normal child, the laboratory evaluation of the proteinuria should be delayed until its persistence is confirmed on repeat urine dipstick testing, preferably on a first morning urine sample (Box 110.1). The child with edema and proteinuria most likely has renal lesions or, more rarely, CHF. Additional findings on examination could include the presence of hypertension, ascites, pleural effusions, or the rash of systemic lupus erythematosus or anaphylactoid purpura.

Box 110.1. Diagnosis of Proteinuria

- Presence of proteinuria on dipstick urinalysis (≥1+ confirmed on 3 occasions)
- Random urine TP/Cr >0.2 or 24-hour urine protein >4 mg/m^2/hour
- Orthostatic proteinuria (assessed through separate measurement of afternoon and first morning urine for TP/Cr)

Edema in the absence of significant proteinuria can occur in conditions that cause hypoproteinemia (eg, liver or inflammatory bowel disease) or during allergic reactions.

Pathophysiology

The glomerular capillaries are adapted to permit the filtration of minimal amounts of plasma proteins, particularly those with a small molecular radius. Approximately 320 mg of albumin and 360 mg of low-molecular-weight proteins are filtered by the glomerular capillaries each day. Ninety-five percent of this material is reabsorbed by the proximal tubular cells. Normally, a child may excrete up to 100 mg/m^2 per day of protein. Urinary protein excretion is increased in newborns to approximately 240 mg/m^2 per day and in adolescents to approximately 300 mg/m^2 per day. Adults may normally excrete up to 150 mg/m^2 of protein per day. Only 10% to 15% of this is albumin; the rest of the proteins are other plasma proteins and urinary glycoproteins, such as Tamm-Horsfall protein.

In cases in which increased proteinuria results from glomerular disease, higher than normal levels of urinary proteins are primarily caused by the enhanced filtration of albumin. Abnormal urinary protein excretion is a marker of chronic kidney disease, and attempts to improve proteinuria with angiotensin-converting enzyme inhibitors or angiotensin receptor blockade in this setting have been shown to slow the progression of glomerular diseases. Protein excretion may be increased transiently by any condition that raises intra-glomerular capillary pressure, such as CHF, strenuous exercise, epinephrine use, fever, urinary infection, and surgery. The child or adult with very early diabetic nephropathy or early end-organ damage from hypertension exhibits an elevated urinary microalbumin-creatinine ratio. The child with diabetes or hypertension should undergo regular testing for the urinary microalbumin-creatinine ratio to detect early, reversible glomerular damage.

Individuals with *orthostatic proteinuria* excrete pathologic amounts of protein in their urine while they are upright, but their urinary protein excretion returns to normal when they are recumbent. Some children are affected by this poorly understood, benign condition. Orthostatic proteinuria seems to be more common in athletic adolescent individuals. Normal children exhibit a diurnal variation in urinary protein excretion, but that variation is exaggerated in children with orthostatic proteinuria. A recent careful study of 91 healthy Hispanic and non-Hispanic white children age 6 to 19 years and living in a city in the American Southwest showed that 19.8% of those children had orthostatic proteinuria. It was more common in boys older than 10 years and in those with a body mass index above the 85th percentile for age. Orthostatic proteinuria may be caused by increased pressure in the renal vasculature while the patient is upright. Several investigators have shown that patients with orthostatic proteinuria have partial obstruction of the left renal vein by entrapment between the aorta and superior mesenteric artery while standing.

Differential Diagnosis

The proteinuria may be physiological (ie, secondary to fever or CHF), transient, orthostatic, tubular (as seen in allergic interstitial nephritis), or glomerular. Aminoaciduria as a form of tubular proteinuria may occur, as occurs in certain inborn errors of metabolism.

Evaluation

History

It is important to elicit a complete history in the child with proteinuria (Box 110.2). When asking about a history of swelling, the physician should note that subtle periorbital edema may be present only in the early morning hours. If the proteinuria is detected at a routine screening examination, the conditions under which the urine was obtained should be determined. The child may have been ill with a high fever or have just participated in an athletic event, such as a track meet.

Physical Examination

The physical examination should include a determination of blood pressure and measurement of height and weight. A careful assessment for edema should be made. The skin should be examined for signs of rash, such as that seen in Henoch-Schönlein purpura or healing impetigo. The joints should be inspected for any sign of swelling or joint inflammation. The abdominal examination should include a careful search for ascites or organomegaly.

Box 110.2. What to Ask

Proteinuria

- Was the mother's pregnancy remarkable in any way? What was the child's birth like?
- Did the child have any neonatal problems that may indicate possible renal damage? Was the child born preterm? Did the child have intrauterine growth restriction?
- Is any swelling apparent in areas such as the ankles, abdomen, or periorbital region?
- Has the child had any recent illnesses, particularly pharyngitis or impetigo?
- Does the child have a history of joint pains and skin rashes? (The adolescent with such history may be at increased risk of having a collagen vascular disease.)
- Has the child had any previous urinary tract infections, urinary abnormalities, or dark urine?
- Does the child have a history of hypertension or weight loss or gain?
- Is the family history positive for renal disease?
- Does the child have diabetes mellitus?

Laboratory Tests

The extent of the laboratory evaluation depends on the child's general health (eg, the child is ill with another problem), the amount of proteinuria on urine dipstick, and whether the child has edema. The suggested evaluation is outlined in Figure 110.1. In the nonedematous, otherwise healthy child with proteinuria on urine dipstick, it is prudent to examine the urine sediment and, if negative, recheck the urine dipstick in a few days. If proteinuria of 1+ is consistently present on 2 or more occasions and no hematuria is evident, a first-stage evaluation by assessing a urine TP/Cr is indicated. If the child is ill with a fever or is hospitalized with a serious illness, it is often appropriate to delay evaluation of the proteinuria until the acute illness is under control, provided no associated hematuria, hypoproteinemia, hypertension, or azotemia is present.

In the healthy ambulatory patient with persistent, isolated proteinuria on dipstick urinalysis on 3 occasions, it is important to quantitate the proteinuria (Box 110.3). This may be done simply by ordering a urine TP/Cr. If the ratio is abnormal (≥0.2), the child first must be evaluated for orthostatic proteinuria, which can be ruled out in several ways. The simplest evaluation involves checking a urine dipstick test on a first-voided morning sample and again on an afternoon specimen. This procedure should be repeated on 2 different days. It is critical to be sure the child empties the bladder before going to bed, because urine produced during the evening when the child is nonrecumbent may contain protein and thus give an inaccurate result from the sample obtained the following morning. If the dipstick test for protein from the morning urine is negative on a concentrated acid urine and if the afternoon sample is positive for protein on

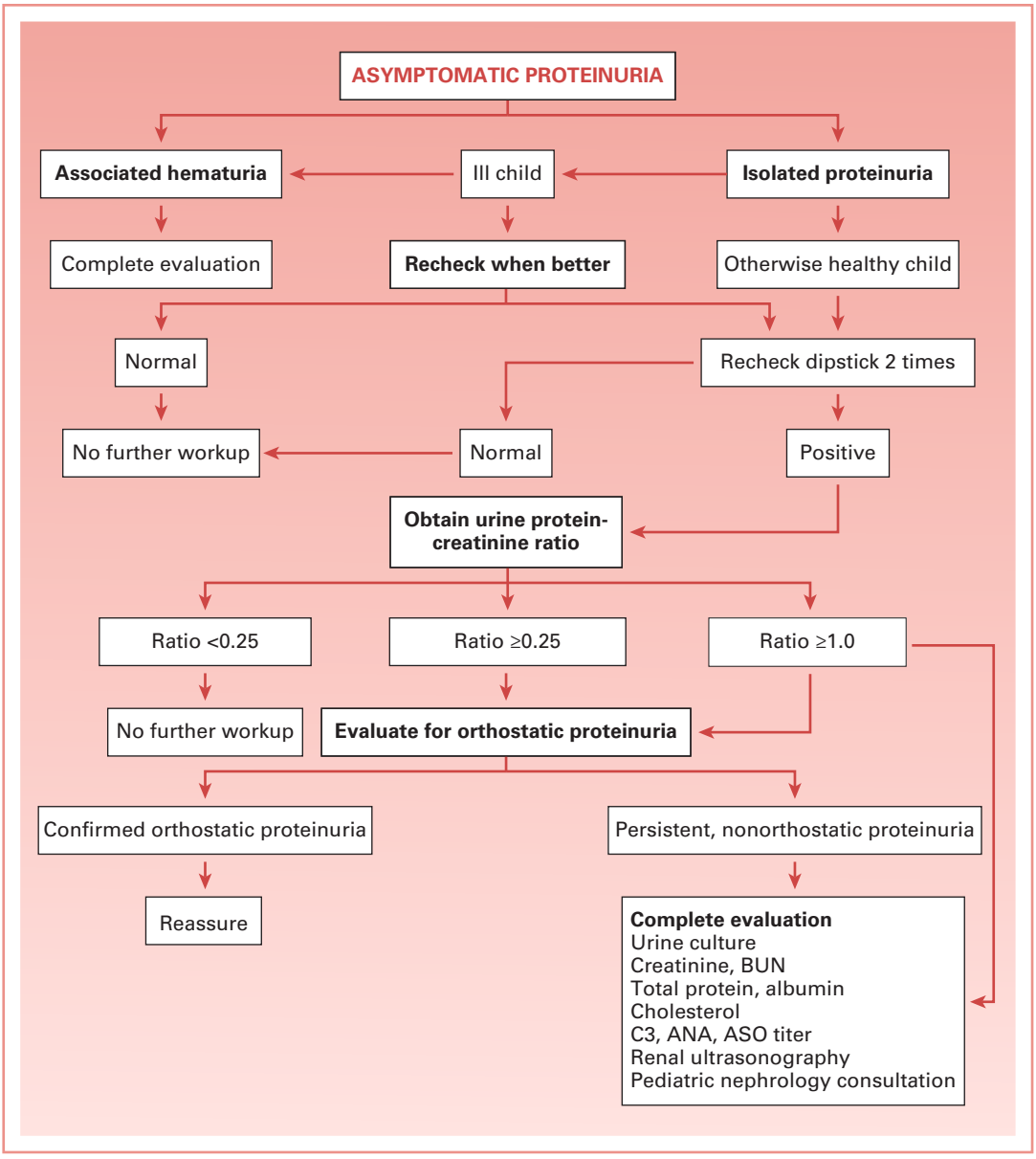

Figure 110.1. Evaluation of children with asymptomatic proteinuria.
Abbreviations: ANA, antinuclear antibody; ASO, antistreptolysin O; BUN, blood urea nitrogen.

Box 110.3. Methods for Assessment of Urinary Protein

Detection of proteinuria by urine dipstick testing is only semiquantitative. This examination is affected by urinary pH and concentration; therefore, more definitive tests are warranted if a patient's urine consistently shows proteinuria on dipstick urinalysis. The sulfosalicylic acid turbidity test is also semiquantitative. When sulfosalicylic acid is added to an aliquot of urine, it precipitates urinary proteins. The amount of turbidity is graded on a scale of 0 to 4+.

Urinary protein is most accurately quantitated by a chemical determination on a timed urine collection (usually 24 hours). The concentration, which is measured in milligrams per deciliter, is multiplied by the total urine volume to determine the milligrams of protein excreted in 24 hours. Twenty-four-hour urine samples are difficult to collect in the young child. However, several studies have shown that a random urine sample for a TP/Cr correlates well with the 24-hour urinary protein excretion. The ratio is determined by dividing the urine protein concentration in milligrams per deciliter by the urine creatinine concentration in milligrams per deciliter. The units must be the same for each component. The urinary TP/Cr is normally less than 0.2. A ratio of 3.5 or greater in an adult or greater than 1.0 in a child is indicative of nephrotic range proteinuria. One study found that proteinuria in combination with leukocyturia (by dipstick testing) likely is indicative of more significant noninfectious renal inflammation.

Occasionally, it is important to determine whether proteinuria has a tubular or glomerular basis. In these instances, a urinary β_2-microglobulin test is helpful. Beta$_2$-microglobulin, a very small protein that is freely filtered at the glomerular level, is nearly completely reabsorbed by the proximal tubules. In instances of tubular injury, such as interstitial nephritis, acute kidney injury, or nephrotoxic renal injury, urinary β_2-microglobulin is increased. With glomerular proteinuria, urine protein electrophoresis shows a heavy preponderance of albumin. The urine microalbumin-creatinine ratio is an excellent indicator of glomerular proteinuria. It is readily available in most laboratories and will detect minimal but pathologic amounts of glomerular proteinuria, such as that seen in early diabetic nephropathy and with early hypertensive glomerular damage.

a concentrated acid urine, the child most likely has orthostatic proteinuria.

A more accurate way of checking for orthostatic proteinuria involves the determination of urine TP/Cr ratios on the first morning and afternoon urine samples. A diagnosis of orthostatic proteinuria can be made if the ratio is normal on the recumbent sample and elevated on the daytime sample. The most accurate (but cumbersome) means of diagnosing orthostatic proteinuria entails collecting 2 timed urine samples, 1 during the hours that the child is up during the day and the other while the child is in bed at night. In most instances of orthostatic proteinuria in children, the total urinary protein excretion is less than 1 g. The urine collected in the recumbent period should contain less than 50 mg/m^2 of protein. If these 2 timed samples meet the criteria for orthostatic proteinuria, it is not necessary to repeat them. It is important to remember, however, that even in renal disease, proteinuria improves somewhat when a patient is recumbent.

If the child does not have orthostatic proteinuria, a 24-hour urine protein excretion may be determined. If the collection of a 24-hour urine sample is impractical, the urine TP/Cr ratio is a reliable alternative. Blood chemistries (eg, blood urea nitrogen, creatinine) should be obtained to determine renal function. Electrolyte status should be assessed with total carbon dioxide as well as serum total protein, albumin, and cholesterol. Serologies should be obtained for antinuclear antibodies, C3, antistreptolysin O titer, and hepatitis B surface antigen if the child comes from a population at risk for hepatitis B.

Twenty-four-hour urine protein excretion should be less than 4 mg/m^2 per hour. The neonate may excrete as much as 150 mg/m^2 per 12 hours, however. Table 110.1 gives a summary of normal urinary protein excretion. If the child has nephrotic range proteinuria or symptoms consistent with nephrotic syndrome (ie, heavy proteinuria accompanied by hypoalbuminemia and hypercholesterolemia), further evaluation is required for nephrotic syndrome (see Chapter 111). If the child does not have nephrotic-range proteinuria, abnormal tubular proteinuria should be ruled out. A normal urinary β_2-microglobulin test rules out tubular proteinuria. Other tubular proteins that may be available using laboratory tests include α_1-microglobulin, retinol-binding protein, and neutrophil gelatinase-associated lipocalin. Generally, consultation with a pediatric nephrologist is recommended if a child has an abnormal 24-hour urinary protein excretion (Table 110.1). If the proteinuria exceeds 1 g per day or if any other minor sign of renal dysfunction or hematuria is present, a biopsy is warranted. A study from Japan showed that in children with constant isolated proteinuria, a urine TP/Cr ratio of >0.5 was predictive of more than minimal glomerular abnormalities on kidney biopsy. Sometimes, the otherwise healthy child with a small amount of isolated proteinuria of less than 750 to 1,000 mg per day is followed by the pediatric nephrologist without a kidney biopsy. However, if this degree of proteinuria persists for 1 year or more, a renal biopsy is warranted.

Imaging Studies

Renal ultrasonography should be obtained to rule out any structural abnormalities but is not indicated in the child with simple orthostatic proteinuria.

Table 110.1. Urinary Protein Excretion by Age

Age	*24-Hour Urine Protein (mg)*	*Urine TP/Cr*
Preterm newborn	14–60	—
Term newborn	15–68	—
2–23 months	17–85	≤0.50
2–4 years	20–121	≤0.2
4–10 years	26–194	≤0.2
10–16 years	29–238	≤0.2

Abbreviation: TP/Cr, ratio of urinary total protein concentration divided by the urinary creatinine concentration.

Management

Most children with normal renal function and normal blood pressure whose evaluation reveals physiological or orthostatic proteinuria should undergo repeat urinalysis on an annual basis. If the proteinuria worsens or if hematuria manifests, a repeat evaluation of renal function is indicated. The child whose initial evaluation reveals persistent, significant proteinuria requires careful follow-up to detect and monitor signs of serious renal disease. This follow-up should include repeat blood pressure measurement and urinalysis every 3 months and repeat chemistries (eg, blood urea nitrogen, creatinine, serum albumin) and urine TP/Cr ratios every 6 months. The child should be treated in consultation with a pediatric nephrologist, whose experience is helpful in reassessing the need for kidney biopsy.

The child with physiological or orthostatic proteinuria who has minimal, persistent proteinuria should be able to follow a full school schedule and be allowed to participate in sports, provided no other contraindications exist. The usual immunization schedule should not be interrupted, and the child should follow a regular diet. No increase in dietary protein is necessary to compensate for the minimal amounts of protein lost in the urine. Results of recent studies in patients with nephrosis have found that a high-protein diet may actually increase urinary protein losses.

Prognosis

The outlook for the child with proteinuria depends entirely on the underlying cause of the proteinuria. The child whose proteinuria is associated with edema or hematuria has an increased likelihood for significant renal disease, such as glomerulonephritis, and the prognosis may be less favorable. If the proteinuria is the result of a form of chronic glomerulonephritis, the child may ultimately develop end-stage renal disease. In the individual with glomerular disease, persistent proteinuria is a strong risk factor for progressive loss of renal function. The child with obesity or hypertension (or both) is at increased risk for developing chronic kidney disease and should be monitored for urinary microalbuminuria as an early marker for kidney disease. If the proteinuria is physiological or orthostatic, however, the long-term prognosis is excellent. Such a child has no greater likelihood than the general population of developing renal functional impairment.

CASE RESOLUTION

It is likely that the evaluation of the healthy teenage boy with isolated proteinuria will reveal that he has orthostatic proteinuria, in which case his long-term prognosis is good.

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CHAPTER 111

Nephrotic Syndrome

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CASE STUDY

A 2-year-old boy is brought to the office because of abdominal distention. He has just recovered from a runny nose that lasted 1 week, with no fever or change in activity. His mother reports that his eyelids were very swollen that morning, and she says that his thighs look "fat." She has noticed that he has fewer wet diapers. He has always been a healthy child, and his immunizations are up to date. The family has a history of asthma and allergic rhinitis. Physical examination shows an active 2-year-old boy. Head and neck examination is clear, except for a few shotty anterior cervical lymph nodes and some minimal periorbital edema. Chest examination reveals some decreased breath sounds at the bases. The abdomen is moderately distended; bowel sounds are active, and a fluid wave is detectable. There is 2+ pitting edema of the lower legs, extending up to the knees. The urine has a specific gravity of 1.030; pH 6; 4+ protein; and trace, nonhemolyzed blood. Microscopic examination shows 4 to 6 red blood cells per high-power field and 10 to 20 hyaline and fine granular casts per low-power field.

Questions

1. What is the differential diagnosis of edema and ascites in previously healthy young children?
2. What criteria are used to determine if children with nephrotic syndrome require hospitalization or can be managed as outpatients?
3. What laboratory evaluation and therapy are instituted initially?
4. What are the important issues to address in parent/guardian education?
5. What is the prognosis of young children with nephrotic syndrome?

Although nephrotic syndrome is not a common childhood disease, every pediatrician can expect to care for 1 to 3 children with nephrosis at some time. Nephrotic syndrome may have serious or even fatal complications, and the disease tends to follow a chronic, relapsing course. Thus, it is important for the pediatrician to become familiar with the signs and symptoms of the disease and with the most current treatment modalities aimed at keeping affected children healthy and active.

Nephrotic syndrome occurs when an individual excretes a sufficient quantity of plasma proteins, primarily albumin, in the urine to cause hypoalbuminemia. Substantial urinary protein losses, hypercholesterolemia, and hypoalbuminemia characterize nephrotic syndrome. The condition is usually accompanied by obvious edema, but occasionally edema is not clinically detectable (Box 111.1).

In children, proteinuria of more than 40 mg/m^2/hour (>50 mg/kg/24 hours) is considered nephrotic range proteinuria. (In adult-sized patients, proteinuria of more than 3.5 g in 24 hours is associated with nephrotic syndrome.) Collection of a 24-hour urine sample is cumbersome in children, and the urinary total protein/creatinine (TP/Cr) ratio done on a random urine sample, preferably a first morning urine, is a useful alternative. Whereas a ratio greater than 3.5 is considered nephrotic range proteinuria in adults with normal renal function, in children a ratio greater than 1.0 may signify nephrotic range proteinuria (see Chapter 110). Twenty-four–hour urine protein losses (g/m^2/day) in children can be estimated by multiplying the urinary TP/Cr by 0.63.

Box 111.1. Diagnosis of Nephrotic Syndrome

- Heavy proteinuria (>40 mg/m^2/hour or 50 mg/kg/24 hours in children)
- Hypoalbuminemia
- Hypercholesterolemia
- Edema

Epidemiology

Minimal change disease (MCD) is the most common form of nephrotic syndrome in childhood. The annual prevalence of new cases of nephrotic syndrome is 2 to 3 in 100,000 children in the population younger than 16 years. The cumulative prevalence of this chronic disease is estimated to be 16 in 100,000. Ninety percent of childhood cases are not associated with any systemic disease, and two-thirds of cases of childhood nephrotic syndrome present before age 5 years. The ratio of boys to girls in young children with nephrotic syndrome is 2:1. By late adolescence, both sexes are equally affected, and diseases other than MCD are much more prevalent in adolescents.

Clinical Presentation

The typical child presenting with nephrotic syndrome is a preschool-age boy who is brought to the physician because he appears swollen to the parents or guardians. Some children are active and

relatively asymptomatic despite the edema, whereas others may be very uncomfortable, with markedly swollen eyelids, abdominal discomfort, scrotal or labial edema, and even respiratory compromise. Usually children have a history of preceding infection, most typically an upper respiratory infection (URI). Children with nephrosis may develop diarrhea secondary to edema of the bowel wall.

Occasionally, children with nephrosis are critically ill because of peritonitis, bacteremia, or, rarely, a major thrombotic episode. Because their immune state is compromised, rapid evaluation and treatment of children with these complications of nephrotic syndrome are essential for survival. The primary peritonitis associated with nephrotic syndrome may be confused with an acute abdomen, such as may be seen with appendicitis. Some children who are experiencing a severe relapse have hypotensive symptoms secondary to intravascular volume depletion.

Pathophysiology

The exact cause of MCD and focal segmental glomerulosclerosis (FSGS) is not known. Recent genetic and biomarker studies suggest that MCD and FSGS are different diseases, although they both exhibit intrinsic structural defects in the glomerular podocyte. For MCD, the best current theory postulates that some stimulus (usually infectious) causes a clone of cells to proliferate and produce 1 or more soluble factors that are toxic to the glomerular epithelial cells (ie, podocytes), which are the cells that maintain the glomerular basement membranes. Active MCD shows a reduction in the net negative charge across the glomerular basement membrane and causes a diffuse abnormality in capillaries throughout the body, resulting in leakage of albumin in the peripheral capillaries and increases in interstitial fluid. The constituents of the glomerular basement membrane and chemicals coating the glomerular epithelial and endothelial cells normally bear a net negative charge. The presence of these negatively charged chemicals creates a charge-selective barrier to filtration. This barrier plays a significant role in the ultrafiltration of macromolecules present in the plasma, enhancing the filtration of molecules bearing a positive electrical charge and retarding the filtration of molecules bearing a negative electrical charge. During episodes of relapse, patients with MCD show a breakdown in the normal charge-selective barrier to filtration, often resulting in massive proteinuria. Kidney biopsies from patients with nephrotic syndrome demonstrate a net reduction in anionic sites during periods of relapse. Additionally, some children have mutations in podocyte proteins (eg, nephrin, podocin) that result in nephrotic syndrome. Children presenting with nephrosis before 1 year of age have a high likelihood of having a genetic mutation causing nephrotic syndrome, and any child with steroid-resistant nephrotic syndrome should also be screened for such genetic mutations.

Recent studies have shown evidence that the soluble factors in FSGS and MCD likely are different. For example, although 70% of patients with FSGS have been shown to have elevated plasma levels of soluble urokinase-type plasminogen activator receptor (suPAR), in patients with MCD the levels are undetectable. Considerable evidence exists indicating that the proteinuria in the patient with MCD or FSGS may be caused by soluble factors. Some patients who develop end-stage renal disease from idiopathic nephrotic syndrome (particularly FSGS) have experienced a relapse of the nephrotic syndrome with massive proteinuria immediately after transplantation of a normal kidney. In 1 instance, a patient with end-stage renal disease from FSGS developed an immediate severe relapse after transplant. The kidney was removed and transplanted into another patient without FSGS, and the kidney functioned normally without proteinuria. Infusion of peripheral blood mononuclear cell products from children with nephrosis induces albuminuria in rats. Removal of serum proteins by adsorption to a protein A Sepharose column or by plasmapheresis has resulted in remission of proteinuria in some patients who have experienced a recurrence of nephrotic syndrome after transplantation. Mixing plasma from a patient in relapse with FSGS with glomeruli in vitro can cause swelling of the glomeruli. The remission of the proteinuria after treatment with immunosuppressive medication provides further evidence that nephrotic syndrome is mediated in some way by the immune system. Children with MCD have been shown to have higher helper T/regulatory T cell ratios than in healthy children.

Normal adults are able to synthesize 12 g (0.4 oz) of albumin per day in the liver, and adults with nephrotic syndrome may synthesize 14 g (0.5 oz) of albumin per day. Therefore, the hypoproteinemia characteristic of nephrotic syndrome cannot be explained completely by measured amounts of urinary protein losses (approximately 3.5 g/day [0.1 oz/day]). The difference between the hepatic synthetic capacity for albumin and measured urinary losses can be explained by protein catabolism in the kidney. Renal tubular epithelial cells reabsorb filtered plasma proteins and catabolize them to amino acids, which then reenter the amino acid pool of the body. Thus, the magnitude of losses of plasma proteins at the glomerular level is far greater than the amount measured in a 24-hour urine sample.

The hypoalbuminemia that occurs in nephrotic syndrome is a result of the massive proteinuria, and the hypercholesterolemia occurs as a consequence of the hypoalbuminemia. The hyperlipidemia is partially the result of a generalized increase in hepatic protein synthesis that also involves overproduction of lipoproteins. Additionally, less lipid is transported into the adipose tissue because the activity of lipoprotein lipase is reduced in adipose tissue during active nephrotic syndrome. Hyperlipidemia is most pronounced in children with MCD. Serum albumin levels and serum cholesterol levels are generally inversely correlated. The hyperlipidemia is the last biochemical abnormality to clear after the child achieves remission from an episode of nephrotic syndrome.

Differential Diagnosis

Nephrotic syndrome is considered primary or secondary. Primary nephrotic syndrome is not associated with a systemic disease, whereas secondary nephrotic syndrome is a feature of a systemic disease, such as anaphylactoid purpura, immunoglobulin (Ig) A nephropathy, or systemic lupus erythematosus (SLE). Most young children with nephrotic syndrome have the primary form of the disease and secondary causes become more prevalent during adolescence.

Children with primary nephrotic syndrome are also classified according to their response to steroid therapy. Affected individuals may be categorized as steroid-sensitive, steroid-dependent, or steroid-resistant. Typically, children who are steroid-sensitive and remain so have MCD; however, a renal biopsy must be performed before the diagnosis of MCD is made. Sensitivity to or dependence on corticosteroids is a critical factor in determining a child's prognosis.

Nephrotic syndrome is also classified by the appearance of the glomeruli on renal biopsy. A summary of the histologic lesions causing nephrotic syndrome appears in Table 111.1. Approximately 95% of young children with nephrotic syndrome have MCD. In these children, light microscopy shows normal-appearing glomeruli. Immunofluorescent microscopy typically is negative but may show some mesangial IgM deposits, and electron microscopy simply shows foot process effacement of the podocytes. In individuals with FSGS, light microscopy may show enlarged glomeruli and glomeruli with segments of sclerosis. Immunofluorescence may reveal some IgM and complement in the sclerotic segments, and electron microscopy shows areas of foot process effacement of podocytes. Biopsies performed later in the disease course show some totally sclerotic glomeruli, areas of interstitial fibrosis, and atrophy. Several recent series have noted an apparent increase in the incidence of FSGS among children with nephrosis.

Other primary renal diseases that can cause nephrotic syndrome in children include membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), IgA nephropathy and other forms of chronic glomerulonephritis, congenital nephrotic syndrome, and diffuse mesangial proliferative glomerulonephritis. Chronic hepatitis B infection may cause membranous nephropathy or MPGN. In endemic areas, the incidence of hepatitis B–associated membranous nephropathy has been reduced since the implementation of universal hepatitis B vaccination programs. Rarely, poststreptococcal acute glomerulonephritis and other forms of postinfectious acute glomerulonephritis may also cause nephrotic syndrome. With the exception of congenital nephrotic syndrome, all these diseases show the presence of immune deposits in the glomerular mesangial regions or along the glomerular basement membrane as well as some element of cellular proliferation, which may be severe. In these disease states, the presence of nephrotic syndrome is indicative of marked injury to the glomerular capillary wall. Neonates with congenital nephrotic syndrome Finnish type have a mutation of the gene encoding the nephrin molecule, a podocyte protein with a large extracellular domain that is an integral part of the glomerular slit diaphragm. These neonates have massive proteinuria beginning in utero and have severe nephrotic syndrome presenting in the first month after birth.

Because of the varying distribution of edema fluid at presentation, nephrotic syndrome may be confused with sinusitis or an allergic reaction (eg, periorbital edema), obesity (eg, ascites), or an abdominal mass (eg, ascites). Other causes of generalized edema, such as congestive heart failure, hypoproteinemia from inflammatory bowel disease, or liver disease, can be easily excluded with routine laboratory testing.

Table 111.1. Distribution of Histologic Type by Age of Onset in Children With Nephrotic Syndrome

Age (years)	MCD[a]	FSGS	MN	MPGN	Other GN
1–4	95%	3%	2%	—	—
4–8	75%	15%	1%	7%	2%
8–16	52%	15%	2%	25%	6%

Abbreviations: FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; MCD, minimal change disease; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis.

[a] MCD remains the dominant histologic type through mid-adolescence but becomes relatively less important in later childhood and adolescence.

Evaluation

History

The clinical evaluation should include a careful history (Box 111.2).

Physical Examination

A complete physical examination is necessary. Blood pressure should be monitored, because hypertension or hypotension may occur. The extent of peripheral and central edema, including swelling of the eyelids, should be assessed. The physician should obtain a reliable, overall impression of the child's level of comfort and activity. Examination also should include a careful search for infection, particularly life-threatening infections, such as pneumonia or peritonitis. Examination of the head and neck should focus on signs of recent infection, such as otitis media. The presence of dullness to percussion at the bases of the thorax is consistent with large pleural effusions. Ascites may be minimal or massive. With severe ascites, scrotal or labial edema may occur. The child with a history of abdominal pain should undergo a careful examination for signs of peritoneal irritation. The skin should be inspected for infection and rashes.

Laboratory Tests

The laboratory evaluation of the child with nephrotic syndrome begins with a urinalysis. The dipstick shows 3+ or 4+ protein,

Box 111.2. What to Ask

Nephrotic Syndrome

- Has the child recently had any infections, such as pharyngitis or an upper respiratory infection? Is the child from a group at high risk for hepatitis B or C infection?
- Are the child's eyelids swollen? Do they look more puffy or less puffy at certain times during the day, especially on awaking or after crying?
- Does the child have a history of rashes characteristic of diseases that are associated with nephrotic syndrome?
- Is there a history of fever, oliguria, or abdominal pain?
- Is there a family history of nephrotic syndrome or kidney disease?
- Is the child playful and active, or is the edema so significant that movement is uncomfortable?
- Are the ascites and pleural effusions so severe that some respiratory compromise is evident?

although a dilute urine may be only 2+. Microscopic hematuria may be present in up to 25% of children with MCD. The presence of associated glycosuria in a child with nephrosis who is not on steroid therapy is concerning for FSGS. Careful microscopic examination of the urine is necessary. Casts are seen frequently, because urinary proteins precipitate in the tubules. The casts are hyaline, fine, and coarse granular. White blood cell (WBC) casts are sometimes seen, because some children with nephrotic syndrome may also have increased amounts of leukocytes in their urine. Large amounts of red blood cells (RBCs) and RBC casts are rarely seen in uncomplicated MCD and, if present, indicate another cause for the nephrotic syndrome. If RBC casts are seen together with substantial hematuria, an antistreptolysin O titer should be added to the preliminary evaluation outlined in this section. A random urinary TP/Cr should be done to determine whether the child has nephrotic range proteinuria.

If the urine shows only proteinuria, with perhaps some microscopic hematuria, blood tests should include a complete blood cell count, serum creatinine and blood urea nitrogen, electrolytes, serum calcium, serum albumin, cholesterol, complement component 3 (C3), and antinuclear antibody. The complete blood cell count may show a high hematocrit from hemoconcentration, because many children experience volume contraction as a complication of hypoproteinemia. Children may also have very high platelet counts (sometimes >1 million/μL). The blood urea nitrogen and creatinine help assess renal function. A hyperchloremic metabolic acidosis is sometimes seen. The serum albumin and cholesterol are required to differentiate nephrotic syndrome from other edematous states. A low level of C3 is associated with other renal diseases, such as MPGN, acute postinfectious glomerulonephritis, and SLE. The antinuclear antibody is useful in screening for SLE and other collagen vascular diseases. Hepatitis B serology is helpful in children who come from a population at risk for hepatitis B infection, such as recent immigrants from Southeast Asia or children of individuals who use intravenous (IV) drugs. Although not part of the routine laboratory evaluation, measurement of quantitative Ig often shows low IgG levels and elevated IgM levels. Blood and urine cultures should be obtained from the febrile child and, if signs of peritoneal irritation exist, a culture of peritoneal fluid should be obtained as well. Although not part of the routine evaluation, family history of thrombotic events warrants consideration of a thrombophilia evaluation because of the association between renal vein thrombosis and nephrotic syndrome, particularly in adults.

Imaging Studies

Chest radiographs help assess the severity of pleural effusions in children with marked ascites and respiratory compromise.

Management

Hospitalization

The decision to admit a child with nephrotic syndrome to the hospital is determined by the child's functional status. Any child with severe edema compromising ambulation or respiration should be admitted. Other indications for admission include unstable vital signs, fever, marked oliguria, and hemoconcentration (hematocrit ≥48%–50%). Most children with nephrotic syndrome who are hospitalized are admitted for control of edema or treatment of a complication, such as infection. A child hospitalized with nephrotic syndrome is likely to have the serious complications of infections, thrombosis, and/or acute kidney injury (AKI).

Management of the child in relapse is focused on minimizing edema and preventing complications until the disease can be controlled with immunosuppressive therapy. Intake, output, and weight must be closely monitored. Blood pressure should be followed, although hypertension is not common. If the child has a fever (temperature >38.2°C [>100.7°F]), blood and urine cultures should be obtained and antibiotics started pending culture results. Because of the risk for AKI, nephrotic medications should be avoided if possible. If signs of peritoneal inflammation are evident, paracentesis should also be performed to obtain samples of ascitic fluid for Gram stain, cell count, and culture. Broad-spectrum antibiotics should be given to cover respiratory pathogens, especially pneumococcus, and enteric pathogens. All children who are newly diagnosed with nephrotic syndrome should undergo a purified protein derivative (PPD) test, because immunosuppression associated with steroid therapy may facilitate reactivation of tuberculosis infection. Treatment with corticosteroids should be delayed until confirmation is received of a negative PPD.

Intravenous albumin (25%) should be used selectively, because albumin infusions are expensive, and the infused albumin is excreted rapidly in the urine. Infusions are indicated in the child with marked ascites, scrotal or labial edema, or significant pleural effusion. Infusions are also helpful in maintaining blood pressure and renal perfusion in the septic child with nephrotic syndrome. The usual dose is 1 g/kg, up to 25 g, infused over 2 to 4 hours, with close monitoring of blood pressure. Furosemide (1 mg/kg IV) is usually administered postinfusion. Albumin infusions may be repeated every 12 to 24 hours as necessary. If urine output does not increase after the first or second albumin infusion in the child with oliguria, immediate assessment for the presence of AKI is required (see Chapter 81). The albumin-induced mobilization of edema fluid in children with nephrosis with oliguria from AKI can precipitate pulmonary edema.

The child with nephrotic syndrome has an increased tendency to thromboembolic phenomenon. Increased risk factors for this complication include loss of antithrombin 3 in the urine, age 12 years or older, the existence of a central line, infection, and secondary causes of nephrotic syndrome (eg, SLE).

Supportive Therapy

Diet

Because sodium plays a key role in edema formation, the child with nephrotic syndrome should be placed on a no-added-salt diet that limits dietary sodium to 2 or 3 g per day. Technically, sodium restriction is indicated only during times of relapse, but a consistent no-added-salt diet helps entire families maintain a healthy diet. Even though children with nephrotic syndrome have hyperlipidemia, it

is not advantageous to implement a low-fat diet, because hyperlipidemia is not caused by fat intake and should resolve after the child goes into remission. In general, fluid restriction is not necessary except in unusual circumstances (eg, a steroid-resistant patient with persistent edema). Although earlier teachings recommended the use of high-protein diets, newer research has shown that high-protein diets may in fact increase urinary protein losses.

Activity

Historically, children with nephrotic syndrome were treated with bed rest because the supine position somewhat reduces urinary protein losses. No evidence shows that bed rest has a significant effect on children's clinical state, however. Thus, most pediatric nephrologists recommend that children be allowed full activity. Boys with marked scrotal edema may be more comfortable resting in bed while diuresis is being initiated. The child with nephrotic syndrome should not be isolated from other children and should be allowed to attend school.

Diuretics

Diuretics are often helpful in children in relapse, particularly in children with steroid-resistant disease. Serum potassium levels, as well as clinical signs of intravascular volume, should be monitored. In the child with moderate intravascular volume contraction, the injudicious use of diuretics could precipitate hypotension and increase the risk of thrombosis and AKI. The most commonly used diuretic is furosemide (1–2 mg/kg per dose given orally or via IV). Spironolactone is sometimes added to the diuretic regimen for its potassium-sparing effect.

Long-term Management

The goal of long-term management is induction and maintenance of remission from active nephrotic syndrome. Throughout treatment, it is important to minimize the side effects of medications. Spontaneous remission may eventually occur in the child with MCD; however, because of the 70% historical mortality rate, waiting for a spontaneous remission is unacceptable. Remissions are induced and maintained with the use of immunosuppressive medications. Figure 111.1 summarizes an approach to the overall management of nephrotic syndrome with these agents. A list of commonly used medications and dosages appears in Table 111.2.

Corticosteroids

More than 90% of younger children with primary nephrotic syndrome respond to corticosteroid therapy. Steroids are, therefore, diagnostic and therapeutic, because failure to respond to steroids can be a marker for disease other than MCD or for a genetic cause of nephrotic syndrome. Some children with MCD are steroid-resistant at some time in their disease, however. Steroids can be started promptly in the child with newly diagnosed nephrotic syndrome if the child has no signs of systemic disease, no more than microscopic hematuria, a normal C3 (or results pending), a negative PPD, and normal renal function. Acute infection should be managed with specific antimicrobial therapy to avoid infection-related steroid resistance.

Prednisone is usually started at 60 mg/m^2 per day. It can be given once a day in the morning or divided into 2 daily doses. Some studies have shown that by treating the first episodes of nephrotic syndrome with a prolonged course of corticosteroids (60 mg/m^2/day for 6 weeks followed by 40 mg/m^2 every 48 hours for 2–5 months), children are subsequently less likely to follow a frequently relapsing course. Proteinuria resolves within 2 weeks in many children with MCD and by 4 weeks in more than 90% of children with MCD. Serum albumin normalizes soon after proteinuria clears, but it may be several weeks before hypercholesterolemia returns to normal. The child who does not respond to 4 weeks of daily prednisone may be treated with a course of IV methylprednisolone at a dose of 15 mg/kg/day for 3 to 5 doses before declaring the child steroid resistant.

The pediatrician can easily manage the steroid-sensitive child, but the child with more difficult nephrotic syndrome should be treated in conjunction with a pediatric nephrologist. The child who experiences relapse is treated with daily prednisone (60 mg/m^2) until the urine is protein-free for 3 days. This regimen is followed by 4 weeks of 40 mg/m^2 every other morning. At the end of that 4-week period the prednisone can be either stopped or tapered off over an additional 2 to 4 months, depending on the child's previous relapse pattern. An increased incidence of side effects (eg, cushingoid appearance, hypertension, obesity, glucose intolerance, glaucoma, cataracts, osteopenia, decreased growth rate) occurs when children require frequent courses of prednisone therapy. In the child who experiences frequent relapses, a chronic course of alternate-day steroid therapy may eliminate relapses and reduce steroid toxicity. Usually prednisone 40 mg/m^2 is given every other morning initially for at least 3 months, which is followed by tapering over the subsequent several months to the lowest dose that maintains the child in remission. A recent study found that children on chronic low-dose alternate-day therapy are less likely to experience a relapse after a URI if they receive daily prednisone at their stable prednisone dose for 7 days during the illness.

Other Agents for Difficult Nephrotic Syndrome

Several other treatment options are available if remission is not maintained with alternate-day steroid therapy or if the child develops signs of steroid toxicity. Historically, cyclophosphamide or chlorambucil were the first agents offered to the child with steroid toxicity. Either of these alkylating agents may induce a long-lasting remission that persists for years in the child with steroid-dependent or frequently relapsing nephrotic syndrome. Either agent is started while the child is in remission on steroid therapy, and the steroids are gradually tapered during the course of treatment with the alkylating agent. Historically, a diagnostic renal biopsy was routine prior to starting an alkylating agent. Currently, many pediatric nephrologists proceed with such therapy in steroid-sensitive or steroid-dependent children without a biopsy, provided that renal function is normal. Although initially a daily dose of cyclophosphamide (2 mg/kg) was recommended for 8 weeks, a 12-week course is more likely to induce a prolonged remission and still be safe. The maximum cumulative dose of

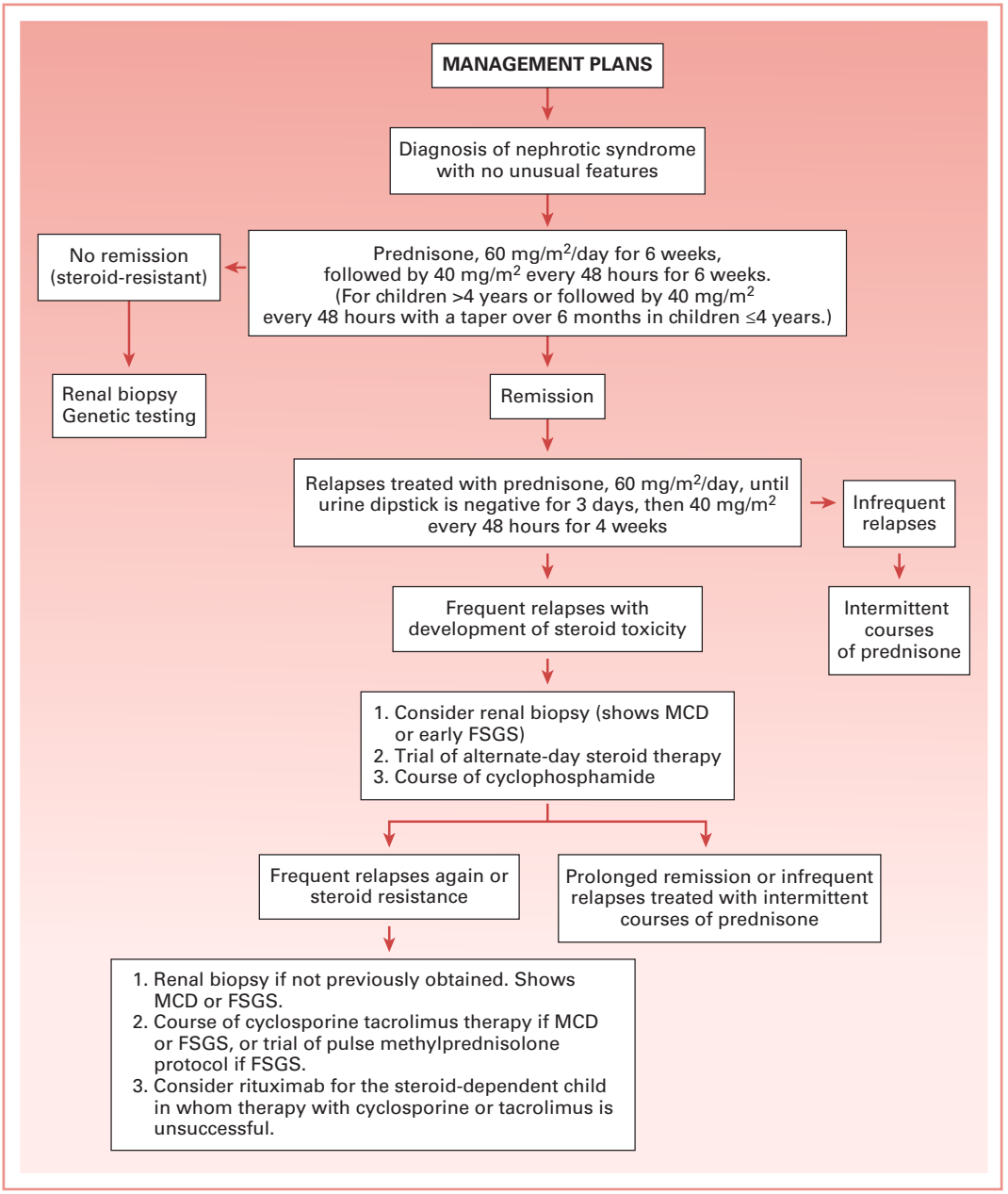

Figure 111.1. Management of nephrotic syndrome in children.
Abbreviations: FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease.

cyclophosphamide should not exceed 168 mg/kg. Chlorambucil at 0.1 to 0.2 mg/kg per day may be given as an alternative to cyclophosphamide, but it may be more toxic.

Potential toxicities of cyclophosphamide include bone marrow suppression with increased risk for infection, alopecia, hemorrhagic cystitis, gonadal toxicity, and possibly a small but indeterminately increased risk of developing a malignancy at some time. Some nephrologists advocate using oral mesna (a medication to miniminize the side effects of chemotheraphy) along with the oral cyclophosphamide to reduce the development of hemorrhagic cystitis. Mesna is always used when individuals receive IV cyclophosphamide. Complete blood cell counts should be monitored weekly, and parents or guardians should be cautioned about the increased risk of overwhelming varicella infections in children who have not yet had a varicella infection or immunization. The cyclophosphamide dose should be withheld if the WBC count falls below 4,000/μL and restarted when the WBC returns to or exceeds 4,000/μL. Alopecia and hemorrhagic cystitis are rare when the recommended dose is used and when children are asked to drink extra fluids while on cyclophosphamide. A 12-week course of cyclophosphamide (2 mg/kg/day) does not seem to increase the risk of infertility, but longer courses are associated with oligospermia, aspermatogenesis, and ovarian dysfunction. Postpubertal individuals may be at greater risk for gonadal toxicity than prepubertal children.

Table 111.2. Treatment Options in Childhood Nephrotic Syndrome

Medication	*Dose*	*Length of Therapy*
Prednisone	Initial course: 60 mg/m^2/day for 6 weeks, then 40 mg/m^2 every 48 hours for 6 weeks	Varies
Cyclophosphamide	2–2.5 mg/kg/day (cumulative dose <168 mg/kg)	12 weeks
Chlorambucil	0.15 mg/kg/day (cumulative dose ≤8.2 mg/kg)	8 weeks
Cyclosporine	2–3 mg/kg every 12 hours, monitor levels, target trough 100–200 ng/mL	Varies
Levamisole[a]	2.5 mg/kg every other day	Varies
Mycophenolate mofetil	12–18 mg/kg every 12 hours; adults, 1–1.5 g every 12 hours	Varies
Tacrolimus	0.05–0.3 mg/day in divided doses, monitor levels, target trough 4–8 ng/mL	Varies
Rituximab	375–1,000 mg/m^2/dose, 2 doses, 2 weeks apart	

[a] Levamisole is no longer available in the United States.

In the child with steroid sensitivity or dependency who has not achieved prolonged remission after cyclophosphamide therapy, a diagnostic renal biopsy is often considered. Renal biopsy is indicated early, however, in the course of illness for the steroid-resistant child. If FSGS is identified on biopsy, treatment may involve a prolonged course of IV methylprednisolone therapy, cyclosporine, or tacrolimus. Therapeutic options for the child with MCD who remains steroid dependent after a course of cyclophosphamide include treatment with mycophenolate mofetil, cyclosporine, tacrolimus, levamisole, or rituximab. Although cyclosporine and tacrolimus are more likely to induce prolonged remission, they maintain remission only while being administered. That is, patients trade steroid dependence for cyclosporine or tacrolimus dependence. Nevertheless, for the child with steroid toxicity, a 12-month course of cyclosporine or tacrolimus allows resolution of the adverse effects of steroids and is generally well tolerated when administered by an experienced physician. Side effects, such as hirsutism and gingival hyperplasia, are frequent at the onset of therapy with cyclosporine. These effects regress as the dose is decreased or the drug is discontinued, however. Hypertension is not uncommon. The most common metabolic abnormality that occurs with cyclosporine use is hypomagnesemia. Long-term therapy may result in significant nephrotoxicity and, rarely, patients experience liver toxicity. Tacrolimus, like cyclosporine, is a calcineurin inhibitor. It has a toxicity profile similar to cyclosporine, but it does not cause gingival hyperplasia or hirsutism and is being used more frequently.

Because of potential toxicity, cyclosporine and tacrolimus should only be prescribed by a physician familiar with the drug. Dosing requirements may change with remission and relapse, and the family and physician should be aware of several drug interactions. Any medication that interferes with the cytochrome P-450 enzyme system in the liver, such as erythromycin, greatly increases cyclosporine and tacrolimus levels and should be used only under extraordinary circumstances. Diarrhea may increase tacrolimus blood levels to a toxic range. The child who requires prolonged treatment with cyclosporine or tacrolimus should undergo follow-up kidney biopsies after 1 or 2 years of therapy to assess for any nephrotoxicity.

Mycophenolate mofetil has been shown to be useful as a corticosteroid-sparing agent in the steroid-dependent, frequent relapsing child. Typically, it is used for at least 12 months because most children relapse if it is withdrawn sooner. Some children have been on this medication for years without apparent adverse events. Levamisole, which is an immune-modulating agent, also has been shown to be useful in the frequently relapsing child. It is not available in the United States, however. Rituximab, an anti-CD20 monoclonal antibody, is also promising for use in the steroid-dependent child. Currently, the use of rituximab should be reserved for the child with continued relapses despite optimal use of prednisone and corticosteroid-sparing agents.

Children with nephrosis who do not achieve good remission with immunosuppressive therapy are given supportive therapy with angiotensin-converting enzyme inhibitors or angiotensin blockers, which reduce proteinuria and have been shown to reduce the progression of glomerulosclerosis. These medications are also first-line therapy for children with nephrosis who develop hypertension. Other supportive measures for children with persistent edema include sodium restriction and the chronic use of diuretics. Genetic testing should be performed early in the steroid-resistant child, and further immunosuppressive therapy should be withheld until the results of the genetic testing are available.

Immunization Issues

Because of the unusual susceptibility to pneumococcal infections, children older than 2 years with nephrotic syndrome should receive the 23-valent pneumococcal vaccine, even if they have previously received the 13-valent conjugated pneumococcal vaccine. The vaccine is best administered while children are in remission, but it produces protective titers even in children who are on alternate-day steroid therapy at the time of immunization. Pneumococcal antibody titers should be measured in patients on multiple immunosuppressive medications, and a second dose of vaccine should be administered to those who do not seroconvert. Influenza vaccine should be administered each autumn to children with nephrotic syndrome using the age-appropriate schedule and dosage.

Some of the routine childhood immunizations (eg, diphtheria-tetanus-pertussis, *Haemophilus influenzae* type b, hepatitis B, inactivated poliovirus vaccine) should be administered by the usual schedule but while the child is in remission, if possible (see Chapter 37). Some controversy exists concerning the use of live-virus vaccines in children who require long-term immunosuppressive therapy.

No vaccines should be administered if a child is currently being treated with an alkylating agent. The measles-mumps-rubella vaccine could potentially cause a relapse. Based on limited data on the use of varicella vaccine in children with nephrosis, it is probably safe to administer varicella vaccine while a child is in remission and not on immunosuppressive medications. It is important to obtain a varicella titer in the child with nephrotic syndrome, because the child who lacks immunity is at risk for overwhelming varicella infection.

Parent/Guardian Education

Because nephrotic syndrome follows a chronic, relapsing course, parent/guardian education is essential for effective long-term management. Parents need to be instructed about using urinary dipsticks to monitor protein excretion. Generally, urine dipsticks should be used daily during periods of active relapse and when medication is being tapered. Otherwise, the dipstick should be checked whenever a child has an infection, including URI; whenever the child looks "puffy"; and weekly when asymptomatic.

Weight should be monitored as well, especially during relapse. The child should be weighed each morning on awaking. Urine output should be measured in more difficult cases. As parents become more familiar with nephrotic syndrome, they will become partners with the physician about medication changes. Parents should also contact the physician about "danger signs," such as fever (temperature >38.2°C [>100.7°F]), significant abdominal pain, and exposure to varicella. If a child does not have protective antibodies against varicella and is taking any immunosuppressive medication (including prednisone), the varicella-zoster Ig should be administered within 72 hours of exposure to varicella. If varicella infection manifests, IV acyclovir should be instituted.

Prognosis

In the preantibiotic era, nephrotic syndrome was frequently fatal, usually because of overwhelming infection. After the introduction of antibiotics, the mortality rate fell significantly. The use of corticosteroids has resulted in a further reduction in mortality. Currently, the mortality rate is approximately 5%, and mortality is caused almost exclusively by infections from encapsulated organisms or thrombosis. The greatest risk of death in children with nephrotic syndrome (approaching 50% over 20 years in some series) is among children with resistance to corticosteroid therapy.

The long-term outlook for most children with nephrotic syndrome is favorable, particularly for steroid-sensitive patients. Relapses often disappear by the completion of puberty. Occasionally, individuals with MCD continue to have relapses into adulthood. Approximately 20% of children with steroid-sensitive MCD still experience relapses 15 years after the onset of their disease. Disease recurrence is highly unlikely if 8 years pass without a relapse. Fewer than 10% of initially steroid-sensitive children with nephrotic syndrome develop end-stage renal disease. This occurs almost exclusively in children with FSGS. Focal segmental glomerulosclerosis may recur after kidney transplants, particularly in young children with aggressive FSGS.

CASE RESOLUTION

The child most likely has MCD. He appears stable enough to be managed as an outpatient and should be placed on a salt-restricted diet and prednisone. The overall prognosis depends on a close interaction among the parents, pediatrician, and consulting pediatric nephrologist.

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CHAPTER 112

Urinary Tract Infections

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CASE STUDY

A 2-year-old girl is brought to the office with a 1-day history of fever (temperature of 39.4°C [103°F]), vomiting, and mild diarrhea. No history exists of any change in her urinary habits, and she still wears diapers. The child has been somewhat irritable but fully alert.

Physical examination reveals an ill-appearing toddler. Her temperature is 39.2°C (102.6°F), heart rate is 122 beats per minute, respiratory rate is 30 breaths per minute, and blood pressure is 90/60 mm Hg. The neck is supple. Head, eye, ear, nose, throat, chest, heart, abdomen, and genital examinations are normal. Urinalysis shows specific gravity of 1.025, pH 6.0, leukocyte esterase and nitrite both strongly positive, protein trace, and blood trace; the sediment has 15 to 20 white blood cells and 2 to 4 red blood cells per high-power field. The Gram stain shows more than 100,000 gram-negative rods, and the urine culture result is pending.

Questions

1. What are the possible diagnoses for the child with positive leukocyte esterase on urinalysis?
2. What are the indications for hospital admission for the child with a urinary tract infection?
3. What antibiotics are used in the management of urinary tract infection?
4. What is the appropriate diagnostic workup for the child with suspected urinary tract infection?
5. When should renal ultrasonography and voiding cystourethrography be done in the child with a urinary tract infection?
6. If the workup is positive for vesicoureteral reflux, how should the child be treated in the long term?

Urinary tract infection (UTI) is among the most common bacterial infections affecting infants and children. Children with UTI frequently present with urinary symptoms such as dysuria, frequency, and urgency. Young infants and toddlers may present with nonspecific symptoms, as with other types of bacterial infection. Further, because of the subtle nature of the symptoms at the early stages of disease, medical intervention may be delayed, resulting in overwhelming sepsis. In most children, UTIs resolve completely with appropriate antibiotic therapy. In the child with an underlying anatomic or functional abnormality of the genitourinary system, such as vesicoureteral reflux (VUR) or bowel-bladder elimination dysfunction, respectively, or with delayed or inadequate antibiotic treatment, however, UTI may result in renal scarring that can sometimes cause hypertension or, rarely, end-stage renal disease.

Urinary tract infection is a nonspecific, generic term implying significant bacteriuria, irrespective of the site of bacterial growth in the urinary tract. In many young children with bacteriuria, clinical findings overlap, and precise classification is not easily made. Some commonly used terms are clarified as follows.

Asymptomatic, covert, and screening bacteriuria are synonymous terms usually used when bacteriuria is detected during surveys of healthy children. The pediatrician should be aware, however, that some affected children, particularly those who are at high risk for developing UTIs, may have subtle urinary symptoms on close questioning. Those children should be treated for UTI using the same principles as used for children who present with obvious symptoms.

Cystitis implies infection of the bladder only. Main features of cystitis are voiding symptoms, such as dysuria, frequency, urgency, enuresis, and foul-smelling urine. Fever, if present, is usually low grade, and the patient may present with lower abdominal pain as well.

Acute pyelonephritis is infection of renal parenchyma characterized by systemic symptoms, such as high fever, chills, flank pain, and vomiting along with voiding symptoms.

Chronic pyelonephritis is a term that has been used in various ways. Ideally, it should be used only to refer to renal scarring resulting from repeated infections as diagnosed based on histologic analysis of renal biopsy specimens. Practically, the term often refers to scarred kidneys as demonstrated by nuclear medicine studies or reduced kidney function.

Urethritis implies infection of the urethra and usually occurs in the setting of sexually transmitted infections. The usual symptoms are dysuria and urethral discharge.

Epidemiology

Bacteriuria is detected in approximately 1% of girls and 2% of boys during routine screening of healthy newborns and young infants in the United States. Approximately 1% of girls continue to have asymptomatic bacteriuria throughout childhood. Bacteriuria in boys older than 1 year is very uncommon. In most affected infants and children, bacteriuria resolves spontaneously with time and does not cause renal damage.

Symptomatic UTI occurs in approximately 2.5% of children annually and accounts for more than 1 million office visits per year. Up to approximately 7% of girls and 2% of boys have culture-proven symptomatic UTI by age 6 years. Before the age of 1 year, UTI recurs in 75% of infants. After 1 year of age, 40% of girls and 30% of boys develop recurrent UTIs following the first episode. In early infancy, UTI is approximately twice as common in boys as in girls and approximately 10 times more common in uncircumcised boys than circumcised boys. After the first 6 months of age, the prevalence of symptomatic UTI becomes considerably higher in females than males, and the difference between circumcised and uncircumcised males disappears. Among vaccinated febrile infants, UTI is the source of fever in approximately 4% to 8% of patients, even in those with symptoms of upper respiratory infection.

Clinical Presentation

Signs and symptoms of UTI in neonates and young infants are usually nonspecific and include fever, irritability, poor weight gain (or weight loss), diarrhea, vomiting, and jaundice. Occasionally, bacteremia or sepsis with temperature instability, cyanosis, and disseminated intravascular coagulation may occur. Older children often have similar signs and symptoms, and often they are able to describe abdominal or flank pain, dysuria, frequency, urgency, enuresis, foul-smelling or cloudy urine, and occasionally gross hematuria (Box 112.1).

Pathophysiology

The pathogenesis of UTI involves interaction between various bacterial factors and protective host factors.

Bacterial Factors

Escherichia coli accounts for 80% to 90% of first infections. The remainder are caused by other gram-negative enteric bacilli (eg, *Proteus, Klebsiella, Enterobacter*) and gram-positive cocci (eg, enterococci, *Staphylococcus saprophyticus*). Rarely, *Morganella morganii, Proteus mirabilis, Providencia stuartii*, and *Serratia* species can cause infection in young children as well. Most organisms that cause UTI originate from the fecal flora. Infections caused by *S saprophyticus*, a coagulase-negative staphylococcus, occur mostly in adolescents with UTI. Nosocomial infection can be caused by *Citrobacter, Enterobacter, Enterococcus,* and *Pseudomonas.*

Box 112.1. Clinical Features of Urinary Tract Infection

- Abdominal pain
- Burning or pain on urination
- Urgency
- Frequency
- Fever
- Leukocyturia or positive nitrite on urinalysis
- Positive urine culture

Microorganisms that cause UTI usually enter the urinary tract by an ascending route. To initiate colonization and infect the urinary tract, these organisms must first adhere to uroepithelium to avoid being swept away during voiding. Bacterial adhesion in *E coli* is mediated by *fimbriae*, which are fine, hair-like proteins emanating from the bacterial cell wall. One important type of fimbriae, P fimbriae, adheres to receptors on the uroepithelium, and some studies have shown that women and children with recurrent UTI have increased numbers of these receptors. In most young children with normal anatomy, acute pyelonephritis is caused by *E coli* with P fimbriae. In most patients with VUR and scarred kidneys, however, the infection is caused by *E coli* without P fimbriae. Thus, the role of P fimbriae in the pathogenesis of renal scarring is uncertain. Additionally, many of these bacteria, which are typically extracellular organisms, can survive and flourish intracellularly by taking advantage of the nutrients of the host cell and evading immune defenses. Other bacterial virulence factors include K and H antigens, colicin, and hemolysin; however, their role in the pathogenesis of UTI is not clearly defined.

Host Factors

Many unalterable host factors contribute to the pathogenesis of UTI, including age, sex, genetics, anatomy, and immune response to infection. Females seem to be at increased risk for UTI because the female urethra is shorter than the male urethra and closer to the anus. As previously stated, the uroepithelium of older girls and adult women who develop recurrent UTI binds *E coli* more avidly than uroepithelium from nonsusceptible individuals. Additionally, individuals with certain P and Lewis blood groups develop more UTIs than others without these specific blood groups. Urinary obstruction or other anomalies may contribute to the development of UTIs in approximately 2% of girls and 5% of boys, especially infants.

Vesicoureteral reflux is the retrograde passage of urine from the bladder to the ureter. After passage through the bladder wall, the normal ureter tunnels under the bladder mucosa for approximately 2 cm before it opens into the bladder lumen. Under normal circumstances, the submucosal segment is compressed when the bladder is filled and during voiding, thus preventing urine backing up into the ureter. Most VUR is primary and caused by a congenital abnormality of the ureterovesical junction, with the ureter having a short submucosal segment and more laterally placed openings. Reflux also may occur in the presence of normal ureteral anatomy when bladder pressures exceed 40 cm of water, as seen in patients with posterior urethral valves or neurogenic bladders resulting from inadequate emptying of bladder creating high pressure inside the bladder and causing leakage of urine back into the ureter. Vesicoureteral reflux is graded on a scale of 1 through 5, with stage 5 being the most severe based on radiologic imaging (Figure 112.1). However, nuclear voiding cystourethrography (VCUG), an alternative study that involves reduced radiation exposure but poor resolution, has been recommended for screening in girls. Because of the poor resolution, however, staging is less precise than with radiologic grading of VUR. Therefore, nuclear VCUG grading has only 3 stages: mild, moderate, and severe.

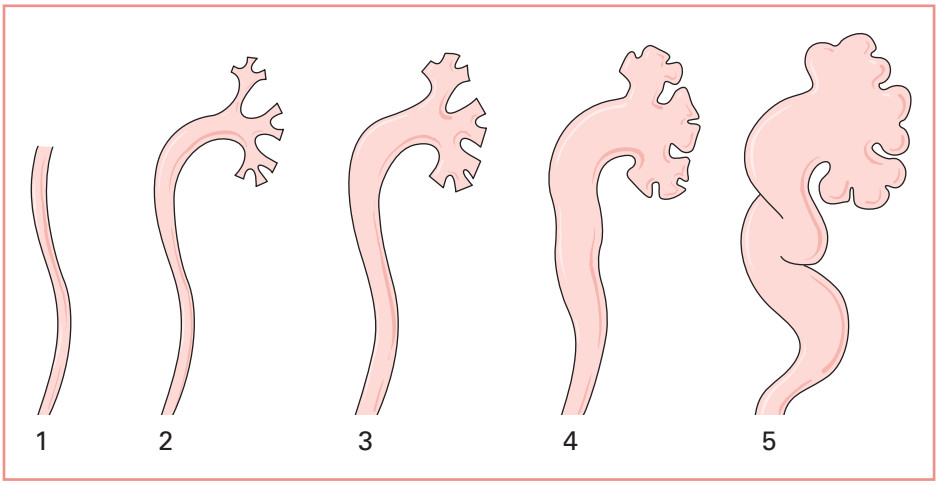

Figure 112.1. Grading of vesicoureteral reflux by vesicoureterography based on international classification. 1, Ureter only. 2, Ureter, pelvis, and calyces, but without dilatation. 3, Mild or moderate dilatation of ureter and mild or moderate dilatation of renal pelvis, but no or slight blunting of fornices. 4, Moderate dilatation or tortuosity of the ureter with moderate dilatation of renal pelvis and calyces and complete obliteration of the sharp angles of fornices, but maintenance of papillary impressions in most calyces. 5, Gross dilatation and tortuosity of ureters, renal pelvis, and calyces; papillary impressions are no longer visible in most calyces.

The incidence of VUR in normal infants is generally stated to be less than 2%; however, recent studies suggest that the incidence of low-grade VUR is much higher, particularly in preterm infants, than previously thought and may be similar to that in older children with UTI. In infants with UTI, the prevalence of VUR is approximately 25% to 50%; in school-age children, approximately 25% to 30%; and in adolescents, approximately 10% to 15%. These findings suggest that VUR often spontaneously resolves with increasing age and maturation of the bladder wall. Vesicoureteral reflux may be a familial disorder and has been reported in 10% to 30% of siblings of index cases. The incidence of UTI is increased in the presence of VUR, likely because of bladder and bowel dysfunction (BBD) or bladder elimination dysfunction resulting in a high amount of residual urine, which refluxes into the ureters or kidneys. This also provides infected urine direct access to the kidneys, which can result in pyelonephritis and, potentially, renal scarring.

It would seem that the greater the severity of VUR in the child with UTI, the greater the likelihood of renal scarring. Recently, however, it has been clearly recognized that many neonates (especially boys) with antenatal VUR, even in the absence of UTI, have congenital dysplastic renal parenchymal defects that had been misidentified as infective scars. Therefore, it is now presumed that the progression of renal scarring in such patients occurs as a result of the natural course of the congenital defect, with or without UTI.

Although many predisposing host factors cannot be changed, several potentially modifiable behaviors related to elimination are associated with UTI in older children. The school-age child with frequent reports of dysuria or recurrent UTIs with no history of UTI as an infant should be questioned for symptoms of *dysfunctional voiding,* a term often applied in the setting of children (especially girls) with no neurologic or anatomic abnormalities but who exhibit abnormal voiding behavior. Such girls often hold their urine for so long that they need to rush to the bathroom, only to incompletely empty their bladder, resulting in urinary stasis and the potential for infection. Additionally, the constipation and abnormal stooling patterns that frequently are associated with dysfunctional voiding are characteristic of BBD. In children between the ages of 6 and 12 years, recent data reveal BBD resulting in diurnal urinary incontinence in 30.7%, holding maneuvers in 19.1%, and urinary urgency in 13.7%, all of which can predispose to UTI.

Differential Diagnosis

In infants and young children, symptoms of UTI are often nonspecific. Thus, a high degree of suspicion for UTI must be maintained. An acute abdomen may rarely be confused with UTI. Some children with dysuria may have chemical irritation from exposure to materials such as bubble baths. A girl with overweight may retain urine in the labial folds, which can cause maceration, urethral irritation, vulvitis, and/or nonspecific vaginitis. Similarly, some young girls do not sit with their legs spread wide enough on the toilet, which can result in reflux into the vagina and cause post-void dribbling with subsequent urethral irritation or vulvitis and/or nonspecific vaginitis. In these patients, urinalysis may be positive for blood or sometimes leukocytes; however, urine culture findings usually help differentiate UTI from perineal flora contamination or vulvitis and/or nonspecific vaginitis or urethral irritation.

Evaluation

History

In all infants and young children with fever without an apparent source, urinalysis, urine Gram stain, and urine culture should be obtained to evaluate for UTI before initiating antibiotic treatment.

If the febrile child younger than 2 years does not appear to be ill, workup should be based on risk assessment. In the older child, a history of fever, dysuria, frequency, abdominal pain, and nausea and vomiting is suggestive of UTI (Box 112.2). The physician should also inquire about any history of previous UTI, abnormal voiding, and constipation.

Bladder and bowel dysfunction is a common risk factor for constipation, urinary incontinence, or enuresis, which can predispose to UTI among school-age children. Lower urinary tract symptoms must be investigated carefully at routine pediatric visits.

Recurrent UTI generally refers to reinfection with a new organism, whether the same or a different species. This is a common problem, especially in the first year after initial UTI. Reinfection with the same organism is infrequent; however, if intermittent symptoms of UTI persist during administration of antibiotics and repeat urine culture is positive after 14 days, the initial infection is characterized as persistent. Persistence is the result of medication noncompliance or inappropriate choice of antibiotic (ie, the pediatrician has not followed up on the sensitivity results and changed the antibiotic accordingly). If symptoms relapse within 2 months even after a negative culture was obtained at 14 days after completion of antibiotic treatment, the condition is characterized as a *relapse* of the previous infection; that is, the infection remained latent and flared after completion of antibiotic treatment. Relapse may be indicative of underlying structural or functional problems of the urinary tract, kidney stones/hypercalciuria, or often, inappropriate antibiotic therapy. If an underlying structural or functional problem is suspected by the pediatrician, appropriate workup should be initiated, and nephrology or urology referral should be made based on those results.

Physical Examination

Weight and height measurements are important to determine whether a patient has a chronic renal condition that may be predisposing to infections, such as obstructive uropathy or neurogenic or nonneurogenic bladder with secondary or primary VUR. The physician should check all vital signs to help determine whether the UTI involves the lower or upper tracts and to assess the severity of infection. An elevated blood pressure and temperature are consistent with an upper tract infection. The abdomen should be examined for masses and tenderness, the genitalia for local lesions, and the lumbosacral area for anomalies (eg, deep sacral dimples, tuft of hair, lipoma, hyperpigmentation, hemangiomas).

Box 112.2. What to Ask

Urinary Tract Infection

Children Age 2–24 Months

- Does it hurt when the child urinates?
- Does the child void with increased frequency?
- Does the urine have an unusual odor?
- Has the child had previous urinary tract infections?
- Does the child have a good urinary stream or urine dribbles?

Children Older Than 24 Months

- Does the child have burning on urination?
- Is the child's urine red or brown?
- Has the child started to wet the bed again?
- Does the child have increased urinary frequency?
- Does the child report abdominal pain?
- Does the child report flank pain?
- Does the child have a fever?
- Does the child have low appetite, or nausea or vomiting?

Laboratory Tests

The diagnosis of UTI is established by documenting significant bacteria in a urine specimen sent for culture. The decision to obtain a urine culture is influenced by the age of the child and the child's symptoms. The factors that influence the likelihood of UTI and the need for a urine study in infants between 2 and 23 months of age are as follows: younger than 12 months, maximum temperature of greater than or equal to 39°C (≥102.2°F), race other than black, female sex or uncircumcised male, and no other fever source. A calculator for more specifically determining the likelihood that an infant in this age group has a UTI can be found at https://uticalc.pitt.edu.

In the young infant, the specimen always should be obtained by bladder puncture or catheterization. Because of the risk of contamination in infants and children, a bag urine sample is not reliable. In the older child with bladder control, a midstream urine collection is satisfactory. The diagnosis of UTI should never be based on the presence or absence of white blood cells alone. Although most older children with symptomatic UTI have pyuria, many neonates and young infants with UTI (25%–50%) may not manifest this finding. Furthermore, leukocyturia may occur in other renal disorders in the absence of UTI. A positive urinary nitrite test is suggestive of UTI; however, the false-negative rate is nearly 50%.

Most patients with UTI (≥85%) have urine bacterial counts greater than 100,000/mL on a voided specimen (ie, significant bacteriuria), although some adult women and teenage girls with symptomatic recurrent UTI have catheterized or "clean catch" urine colony counts less than 1,000/mL. Generally, colony counts of less than 1,000/mL have not been observed in young children with UTIs. Colony counts between 10,000 and 100,000/mL obtained via clean catch are generally unlikely to be significant unless the child has symptoms of UTI, associated leukocyturia, or cultures that are pure growths of a single organism. Any growth of an organism from a suprapubic tap is considered significant. A colony count of at least 10,000/mL in a sample obtained by catheterization is usually necessary to diagnose a UTI. In most children with UTI, however, urine collected by either of these techniques grows more than 50,000 organisms/mL.

The C-reactive protein level usually is increased in the infant or child with high fever and clinical findings suggestive of acute pyelonephritis. Several other laboratory studies, including erythrocyte sedimentation rate, urinary lactic acid dehydrogenase isoenzymes, urinary concentrating ability, and antibody-coated bacteria, have been used with varying success to differentiate upper (ie, renal) from lower (ie, bladder) UTI in older children and adults. Overall,

the reliability of these studies in pediatric patients, especially infants and young children, is not adequate to recommend their routine use. More recently, testing of serum procalcitonin levels has been tried, and preliminary studies suggest that an elevated serum procalcitonin level may have some predictive value in diagnosing pyelonephritis and VUR.

Imaging Studies

Although controversy exists concerning the recommendations, the most recent position statement from the American Academy of Pediatrics (AAP), which was published in 2016, recommends that children younger than 2 years should undergo renal and bladder ultrasonography after the first UTI. Routine VCUG should not be performed unless evidence exists of hydronephrosis, scarring, other anomalies suggestive of obstructive uropathy or high-grade reflux, other atypical complex situations, or recurrent UTIs. If renal or bladder ultrasonography reveal hydronephrosis suggestive of VUR or obstruction, further studies (eg, VCUG, nuclear scan [MAG III], or both) are warranted (Box 112.3).

When febrile UTI recurs and the decision is made to obtain a VCUG, nuclear VCUG rather than contrast VCUG is an acceptable alternative for girls. If indicated, VCUG may be performed after the UTI has resolved; if resolution has not occurred, the study should be delayed 4 to 6 weeks depending on the clinical circumstances. According to the AAP guidelines, antibiotic prophylaxis must be administered until completion of the studies. Excretory urography (ie, intravenous pyelography) is no longer recommended.

Because of a shortage of the technetium Tc 99m succimer (DMSA) in the United States, renal scanning is no longer used to differentiate upper from lower tract UTI or to identify renal scarring. To rule out renal scarring in a child with recurrent UTI, high-resolution Doppler renal ultrasonography or power Doppler renal ultrasonography can be done; these studies detect scarring by delineating the area with poor blood flow.

Management

Per the 2016 AAP reaffirmation of the guideline on diagnosis and management of UTI in febrile infants and young children age 2 to 24 months, for girls the risk factors associated with UTI are white race, age younger than 12 months, temperature at or above 39°C (≥102.2°F), fever for more than 2 days, and no source of infection, and for boys the risk factors are uncircumcised status, race other than black, temperature at or above 39°C (≥102.2°F), fever for more than 24 hours, and no other evident source of infection.

After UTI is confirmed or if the level of suspicion for UTI is high, based on the previously described risk assessment by the pediatrician, all newborns and infants younger than 2 months with a UTI should be treated with parenteral antibiotics, starting with broad-spectrum antibiotic coverage, such as ceftriaxone, cefotaxime, or ampicillin and gentamicin, pending results of sensitivity studies. Infants and children 2 months and older who appear well and can tolerate liquids may receive oral antibiotics on an outpatient basis. Most physicians recommend cephalexin for the first infection until the results of bacterial sensitivity tests are available; treatment is continued for 10 days. For the older child with a high likelihood of UTI based on the risk assessment, antibiotics can be initiated after obtaining a urine culture; otherwise, observation is acceptable until the culture results are available.

In the adolescent with a clear-cut lower UTI, a shorter course of combination trimethoprim and sulfamethoxazole is also effective. The physician should be aware of the local *E coli* resistance patterns, because some communities have a high incidence of *E coli* resistant to this combination. The child who appears toxic or is vomiting should be admitted to the hospital and started on parenteral antibiotics until clinical improvement is evident, at which time the child can be sent home on oral therapy. In the child with a complicated UTI, an infectious disease specialist should be consulted about any questions of the susceptibility and resistance pattern of the urinary pathogen; this specialist also can be consulted about selecting the appropriate antibiotic. A pediatric nephrologist or urologist ultimately should decide on the treatment plan, particularly concerning duration of therapy and follow up (Box 112.4).

Recent studies indicate that continuous antibiotic prophylaxis (CAP) is not necessarily preventive for infection or renal scarring and may cause increased risk for resistant infections with resistant bacteria. However, the physician may decide to treat the child with recurrent UTI (with or without VUR) with low-dose antibiotics (ie,

Box 112.3. Indications for Voiding Cystourethrography

- Prenatal ultrasonography demonstrates moderate to severe hydronephrosis that is confirmed on postnatal ultrasonography
- Detection of bilateral hydronephrosis, in newborn boys
- Child with a history of recurrent urinary tract infection and elevated serum creatinine level with no obvious predisposing factor detected on renal and bladder ultrasonography
- History of severe pyelonephritis in a patient with bladder elimination defect or bladder and bowel dysfunction
- The older child with a long history of recurrent urinary tract infections and bed-wetting

Box 112.4. Indications for Hospitalization for Urinary Tract Infection

- Not tolerating intake orally
- Failed outpatient management
- Impending septic shock
- Dehydration
- Abnormal kidney (ie, single kidney, polycystic kidney disease, chronic glomerulonephritis)
- Immune disorder
- Marked elevation of inflammatory markers (ie, white blood cell count, C-reactive protein level, procalcitonin level)
- Concern about ability of the parent or guardian to follow outpatient management recommendations

trimethoprim and sulfamethoxazole, cephalexin, or nitrofurantoin) for 12 to 18 months after treatment for an acute infection. A recent study examined the outcome between early discontinuation of CAP versus a traditional 2-year course of antibiotics until a child achieves 5 years of age and found early discontinuation to be equally beneficial as the earlier recommendation of long-term CAP. If breakthrough infections occur during the short course of CAP, however, that treatment can be continued for a longer period. Sometimes, the parent or guardian prefers to continue prophylaxis until the child is mature enough to understand the consequences. Provided these children receive close surveillance and follow both physician recommendations and parental guidance, many begin to consume more water (≥1–2 L/day for young children and 2–4 L/day for teenagers), practice proper bladder and bowel habits, and ultimately become infection free for years or stop developing further infections. For the child who develops UTI despite close surveillance and monitoring, it is important for the physician to reevaluate the child for renal scarring and monitor blood pressure closely for developing hypertension.

Indications for referral to subspecialty services, such as pediatric nephrology or urology, depend on the type of practice, type of insurance coverage, and, more frequently, whether the child has complicated or recurrent UTI without an obvious predisposing factor.

Surgery is not necessary in most infants with VUR, including many with severe disease (grades 4 and 5), because most cases of grade 1 through 3 and some cases of grade 4 and 5 reflux in infants resolve with increasing age. In the child older than 5 years with grade 4 or 5 reflux, the rate of resolution with medical treatment is much lower (approximately 20%–25%). The results of the Randomized Intervention in Children with Vesicoureteral Reflux (RIVUR) study show no difference in the rate of renal scarring between prophylactic medical treatment and surgery. Therefore, surgical reimplantation of the ureter is usually recommended only for those patients with poor adherence to antibiotic prophylaxis or with breakthrough infections, especially if the upper tract is involved. This latter group seems to have benefited the most from surgery. If diagnosis of correctable anatomic genitourinary anomaly, such as ureteropelvic junction obstruction or ureterovesical junction obstruction, is made, however, pediatric urology and nephrology specialists should be consulted.

An alternative to surgical reimplantation is dextranomer microspheres (eg, Deflux), a gel composed of dextranomer and hyaluronic acid that can be injected endoscopically into the ureter. It was approved by the US Food and Drug Administration in September 2001 after having been used extensively throughout Europe with great success.

Prognosis

In most children, UTI is a minor illness with few long-term or serious consequences. However, UTI commonly reoccurs, especially during the first year after the initial UTI. For all children, repeat urine cultures should be obtained during follow-up assessments at the completion of antibiotic treatment to avoid inadequate treatment, because some children may require more than the typically prescribed 10- to 14-day course of antibiotics.

Risk factors for the development of renal scarring and eventual hypertension or, rarely, renal failure, include young age (<1 year), recurrent episodes of acute pyelonephritis, delay in starting effective antibiotic therapy, high-grade VUR, BBD, and neurogenic bladder. Increased vigilance in recognizing UTI and provision of appropriate treatment, including follow-up care, would substantially reduce or even obviate these devastating consequences in children with the particular risk factors. Compared with children age 5 years and older, infants and children younger than 2 years with recurrent UTI and high-grade VUR are more likely to develop calyceal clubbing and renal scarring. Renal scarring following UTI may be mitigated by CAP, especially in children with low-grade VUR. However, despite the findings of the RIVUR study that showed a decrease in the number of recurrent infections using CAP compared to placebo, renal scarring was not prevented at 2-year follow up. Because of this, children with recurrent UTIs should be referred to subspecialty services, either pediatric nephrology or urology, for closer surveillance and management (Box 112.5).

Box 112.5. Indications for Subspecialty Referral of the Pediatric Patient With Urinary Tract Infection

- >2 new febrile urinary tract infections in 6 months or >3 new febrile urinary tract infections in 12 months
- A history of urinary tract anomaly or newly diagnosed urinary tract anomaly (eg, severe hydronephrosis, bilateral vesicoureteral reflux, kidney stone disease)
- Single kidney
- Cystic kidney disease
- Spina bifida or neurogenic bladder of any etiology

CASE RESOLUTION

The girl is hospitalized because of the vomiting. She is started on intravenous ceftriaxone and improves in 48 hours. Inpatient renal ultrasonography is normal, and she is discharged home with oral antibiotics. Because this is her first episode of UTI and because ultrasonography was normal, VCUG is not indicated. No consideration is given to prophylactic antibiotics because of her history and normal results on renal ultrasonography.

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PART 10

Orthopedic Disorders

CHAPTER 113

Developmental Dysplasia of the Hip

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CASE STUDY

A 4-month-old girl is seen for her routine health maintenance visit. She is doing well and has no complaints. The results of the entire examination are within normal limits except for limited external rotation and abduction of the left hip, which is approximately 45°, in comparison to that of the right hip, which is almost 90°.

Questions

1. What factors are responsible for normal growth and development of the hip joint?
2. What specific physical maneuvers help in the evaluation of infants with decreased range of motion of the hip?
3. What are the clinical findings of hip dislocation during and after the neonatal period?
4. What are some conditions associated with hip dysplasia that may be noted on physical examination?
5. What is the appropriate diagnostic workup of infants with suspected hip dysplasia?

Developmental dysplasia of the hip (DDH) is a common pediatric orthopedic concern that requires a thorough understanding of normal development, pathoanatomy, natural history, and management. Although historically referred to as "congenital dislocation of the hip," the term was changed because *developmental dysplasia of the hip* defines a spectrum of hip pathology, from congenital dysplasia of the hip, to partial dislocation of the femoral head (ie, hip subluxation), to acetabular dysplasia, to complete dislocation of the femoral head from the true acetabulum. Developmental dysplasia of the hip may exist at birth or manifest during infancy. In a newborn with true congenital dislocation of the hip, the femoral head dislocates into and out of the acetabulum. In an older child, the femoral head remains dislocated, resulting in secondary changes in the femoral head, the acetabulum, and the lateral pelvic wall where the displaced femoral head articulates with it. When DDH is recognized and managed appropriately, the affected child has the potential for normal development. If the diagnosis is missed or delayed, however, the child may suffer significant morbidity, including severe degenerative hip disease.

Epidemiology

The prevalence of DDH is 1% to 7% of all live births. Ethnic variations exist; the incidence in Native American and black individuals is 76 and 0.06 per 1,000 live births, respectively. The literature indicates that pediatricians and orthopedic surgeons diagnose DDH in 8.6 per 1,000 live births and 1.5 in 1,000 live births, respectively. The use of ultrasonography in the evaluation of an infant with suspected DDH has resulted in the diagnosis of DDH in 25 in 1,000 live births. Hip instability in the neonate is estimated to range from 11.5 to 17 per 1,000 live births. Approximately 60% of these cases resolve by 1 week of age, and 90% resolve by 2 months of age. Approximately 60% of infants affected by DDH are firstborn.

Females are affected up to 7 times more frequently than males as result of estrogen-induced ligamentous laxity in utero. The prevalence of DHH is greater in infants with higher birth weights and those who are postmature. Approximately 20% of all DDH occurs in infants born in the breech position. A positive family history of DDH increases the risk by 10%. A female born in the breech position has a 1 in 35 chance of having DDH.

The left hip is involved in 60% of children with DDH and the right hip in 20%, and bilateral involvement occurs in 20% of such children. Developmental dysplasia of the hip has an increased association with lesions of mechanical molding, such as congenital torticollis (approximately 8% of affected children may have DDH), metatarsus adductus (approximately 2%–10% of these children may have DDH), and talipes calcaneovalgus.

Clinical Presentation

The clinical presentation and signs of DDH in children vary with age. In neonates, diagnosis is made primarily by the physical examination (eg, Ortolani maneuver, Barlow maneuver). Classic signs of DDH in older infants are asymmetric skin folds, limitations demonstrated in hip abduction, and a positive *Galeazzi sign*, that is, unequal knee height when the patient is supine with both the hips and the knees flexed. Physical signs, which become more obvious after children are walking, include waddling gait, limping, and toe walking (Box 113.1).

Box 113.1. Diagnosis of Developmental Dysplasia of the Hip

- Breech presentation
- Oligohydramnios
- Female sex
- Positive family history or ethnicity
- Persistent hip asymmetry (eg, asymmetric skin folds, abduction of 1 hip and adduction of the other hip)
- Lower limb deformity (eg, limp, toe walking)
- Torticollis

Pathophysiology

Developmental dysplasia of the hip encompasses a wide variety of conditions ranging from hip instability to dislocation. Normal growth and development of the hip joint is dependent on a genetically determined balance of growth of the acetabular and triradiate cartilages and a well-located and centered femoral head. In a normal hip at birth, a tight articulation exists between the femoral head and acetabulum; however, in DDH or dislocation, this tight articulation is absent. Dysplasia refers to either a hip that is dislocated but can be relocated, or a hip with a positive Ortolani sign (ie, it can be dislocated on provocation). The term *dislocation* refers to any hip with a negative Ortolani sign, that is, the hip is not reducible and is associated with secondary adaptive changes, such as shortening, decreased abduction, and asymmetric skin folds.

Dysplasia of the acetabulum is also associated with hip instability. The dysplastic acetabular cavity is more shallow, with a more vertical inclination angle (Figure 113.1). Although most dislocations occur at or near the time of delivery, this abnormal development of the acetabular cavity helps explain why dislocations can also occur later in infancy. Late hip dislocations are reported in 3% to 8% of affected infants.

The etiology of DDH is poorly defined but is thought to be multifactorial, involving genetic and intrauterine environmental factors. Newborns with a first-degree relative with a history of DDH have a 12-fold increased risk of DDH. The primary intrauterine environmental factors are tight maternal abdominal and uterine musculature; breech presentation, which causes abnormal hip flexion and resulting dislocation of the femoral head; and positioning of the fetal hip against the mother's sacrum, causing increased femoral adduction and resulting in dislocation of the femoral head. In utero mechanical factors relate to molding and restriction of fetal movement. It is believed that the tight, unstretched maternal abdomen and uterine musculature of the primigravida may restrict fetal movement, thereby predisposing firstborn infants to DDH. The increased occurrence of other conditions thought to be secondary to molding (eg, congenital muscular torticollis) with DDH supports this theory of space restriction. Physiologic factors are related to ligamentous laxity and inherent instability of the hip at birth. In utero, a growth rate discrepancy exists between the femoral head and the acetabulum. The femoral head grows more rapidly, and at birth only 50% of the femoral head is covered by the acetabulum. Additionally, diffuse ligamentous laxity exists in the final 4 weeks of gestation in preparation for birth, including laxity of the hip capsule. Female infants may be even more sensitive to maternal hormones, such as estrogen and relaxin, which are thought to be responsible for this generalized physiologic laxity. Environmental factors that may predispose infants to DDH include swaddling with the legs in extension and adduction, which is still practiced in some societies (eg, use of cradleboards by Navajo individuals in North America). Such swaddling was also practiced in Japan until 1975, and after teaching proper swaddling methods, the incidence of DDH decreased fivefold. Other factors include muscle contractures resulting from neuromuscular disease, such as cerebral palsy.

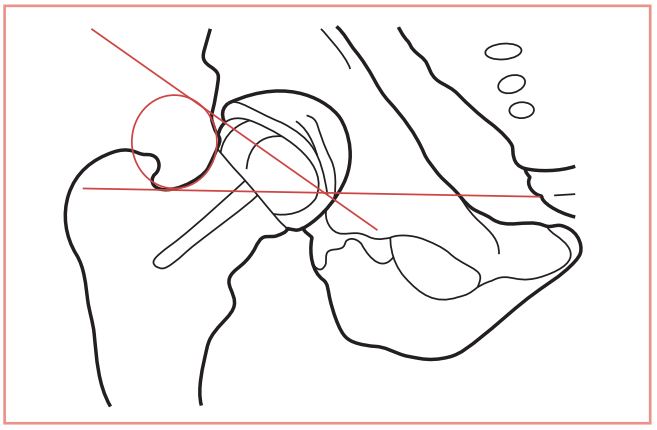

Figure 113.1. Illustration shows the increased inclination angle characteristic of developmental dysplasia of the hip. The more vertical orientation of the acetabulum (compared with normal) results in a less stable hip articulation.

Differential Diagnosis

The differential diagnosis of hip dysplasia depends on the age of the child and the presenting complaint. An infant may have a "click" on abduction of the hip that represents the snapping of a ligament rather than the reduction of the dislocated hip into the joint. An infant with limited abduction may have a neuromuscular disorder, such as spastic diplegia, a form of cerebral palsy that affects the lower extremities. The older child who presents with a gait disturbance, such as limp, waddling gait, or toe walking, may have a neuromuscular condition, fracture, or infection (eg, osteomyelitis, septic arthritis).

Evaluation

History

Family history of DDH should be reviewed, and a careful neonatal history should be obtained, including presentation (eg, breech versus vertex), type of delivery, history of prenatal problems (eg, oligohydramnios), history of neuromuscular disorders (eg, cerebral palsy) and presence of congenital torticollis or metatarsus adductus (Box 113.2).

Box 113.2. What to Ask

Developmental Dysplasia of the Hip

- Was the infant in a breech presentation?
- Does the child have any muscular problems, such as torticollis?
- When did the gait disturbance begin?
- Does anything make the child's gait better or worse?
- Is the child in any pain?
- Did any member of the family have hip dysplasia?

Physical Examination

It is important to evaluate the hip joint for instability or dislocation throughout the first year after birth or until the child begins to walk. It is important to assess the patient for other causes of hip instability as well, because a diagnosis other than DDH may require a different treatment approach and prognosis. For example, a neurologic examination should be performed to assess for spasticity associated with cerebral palsy, a spine examination to assess for torticollis, a cutaneous examination to assess for changes associated with spinal disorders (eg, spina bifida), and a foot examination to assess for conditions such as metatarsus adductus. The Ortolani maneuver and the Barlow maneuver may be used in the neonatal period to evaluate for DDH (Figure 113.2). Both tests are performed with the infant positioned supine and the hips and knees flexed to 90°. The infant should be quiet and relaxed, because both tests require a cooperative child for adequate results.

The Ortolani maneuver, also referred to as the "click of entry," is a diagnostic test used to detect reduction of a dislocated femoral head. To perform the test, the examiner gently abducts the hip and lifts the femoral head anteriorly. A positive sign is a palpable "clunk," felt when a dislocated femoral head is reduced. This "clunk" differs from the audible hip click, which is the result of nonpathologic processes, such as ligamentous snapping. Each leg should be examined separately, not simultaneously.

The Barlow maneuver, also referred to as the "click of exit," is a diagnostic test that is used to identify a dislocatable femoral head in an unstable or dysplastic acetabulum. To perform the maneuver, the hips are adducted, and a posterior force is placed along the longitudinal axis of the femur. Subluxations or dislocations are readily palpable. The Ortolani and Barlow maneuvers are rarely used after 6 to 8 weeks of age because the surrounding soft tissues and muscles adapt to the dislocated hip, making it more difficult to reduce.

If the diagnosis of DDH or dislocation is not made shortly after birth, a different set of physical findings exists, including asymmetry of hip abduction secondary to adductor muscle shortening as well as contracture on the affected side. Limited hip abduction is the most reliable late diagnostic sign of DDH.

As the femoral head dislocates posteriorly, the thigh is shortened on the affected side, producing relative limb shortening and asymmetry of the gluteal, thigh, and labial folds. Asymmetric gluteal folds may result from bunching of skin and subcutaneous tissue on the affected side; however, asymmetric skin folds have not been shown to be uniformly predictive of DDH and assessment for DDH requires further evaluation. The *Galeazzi sign* is noted when the femoral head displaces laterally and proximally, causing apparent shortening of the femur on the affected side. On examination, a positive Galeazzi sign may be observed with discrepancy in knee heights noted when infants are supine, with the sacrum flat on the examination table and the hips and knees flexed (Figure 113.3).

In the child of walking age, the physician may notice a limp because of the relative leg length discrepancy. A child may try to disguise the limp by toe walking. A Trendelenburg test may be positive. Normally, when a child stands on 1 leg, the hip abductors straighten

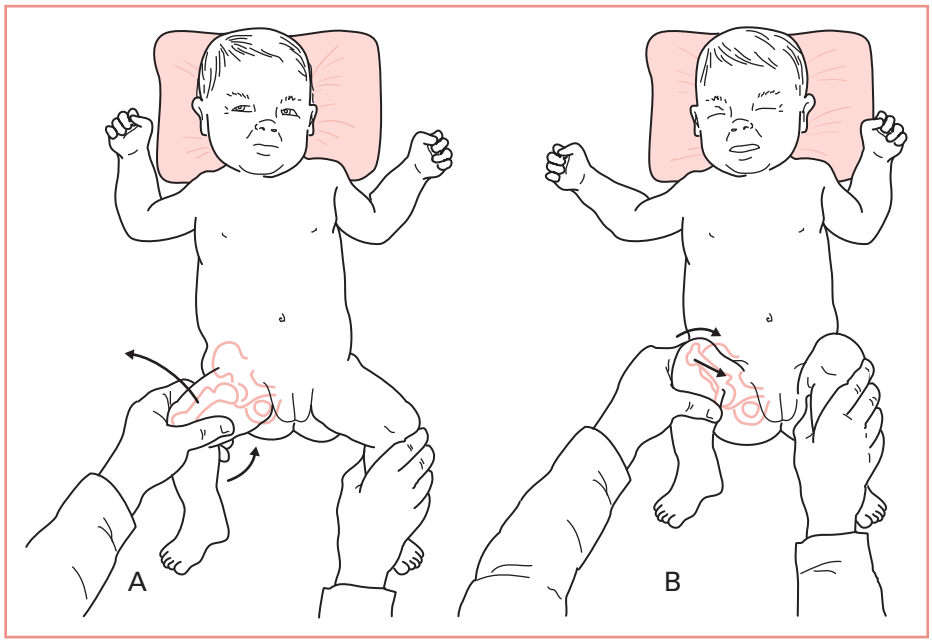

Figure 113.2. Illustration of the Ortolani and Barlow maneuvers. A, Ortolani (reduction) maneuver. B, Barlow (dislocation) maneuver.

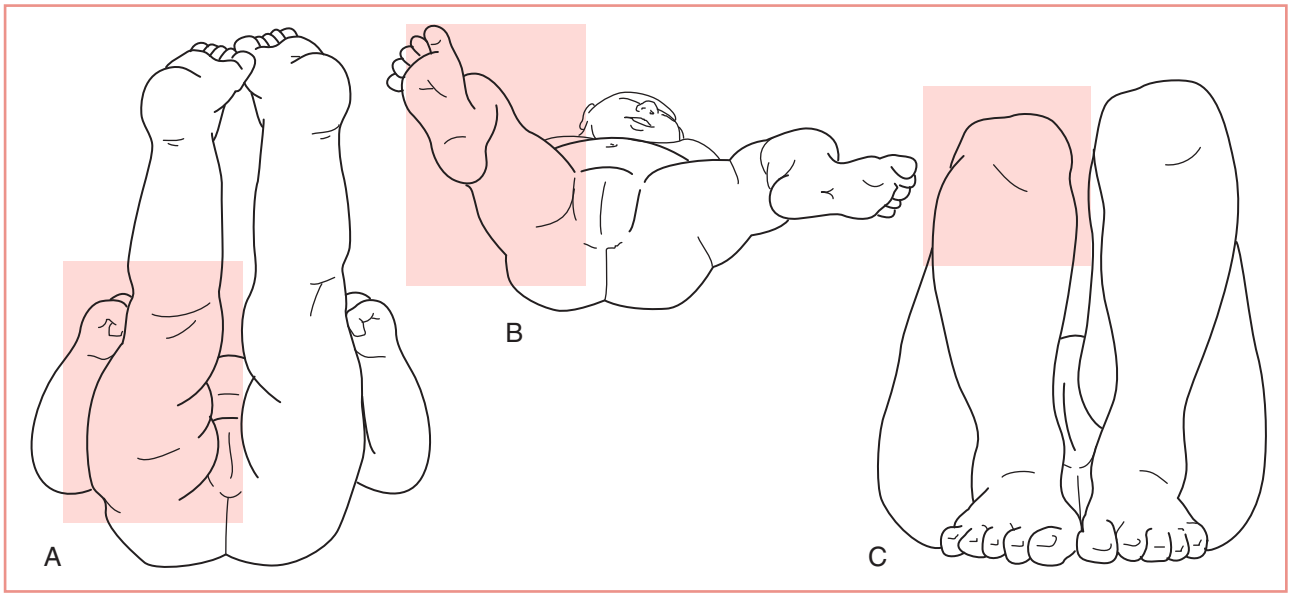

Figure 113.3. Late signs in the diagnosis of developmental dysplasia of the hip. A, Asymmetry of thigh folds. B, Asymmetry of hip abduction. C, Discrepancy of knee heights.

the pelvis and keep the center of gravity over the femoral head. If the abductors are weak, the weight shifts to the opposite side, causing it to droop. The gait abnormality classically associated with unilateral hip dislocation in a child of walking age is called the Trendelenburg gait. In contrast, a child with bilateral hip involvement may display hyperlordosis and a waddling gait.

Imaging Studies

Radiologic and ultrasonographic evaluations may aid in the diagnosis. Hip ultrasonography is helpful to confirm the diagnosis and identify more subtle forms of the disorder. In some European countries, ultrasonography is used as a primary screening modality; however, in the United States the recommendation is to restrict its use to the high-risk infant (ie, female born breech) or an infant with a click that has not resolved after 2 weeks of observation. Dynamic ultrasonography is the only diagnostic test that allows real-time evaluation and a 3-dimensional view of the neonate's hip as it is being manipulated. Reliable radiographic changes begin to become evident by 4 to 6 months of age when the ossific nucleus of the femoral head appears in most infants (Figure 113.4). A flat, shallow acetabulum and delayed ossification of the femoral head are the simplest and most easily recognizable findings. Ultrasonography is primarily used before 6 months of age and radiography at age 6 months and older because 80% of infants have adequate femoral head ossification after 6 months of age. It is recommended that dynamic ultrasonography be used only during the initial and final evaluations, because interobserver differences may result in unnecessary or potentially harmful changes in treatment.

Classification

A primary means of classifying dysplasia of the hip is the Graf classification system, which combines many factors, including age as well as the cartilaginous/boney roof and rim angles of the

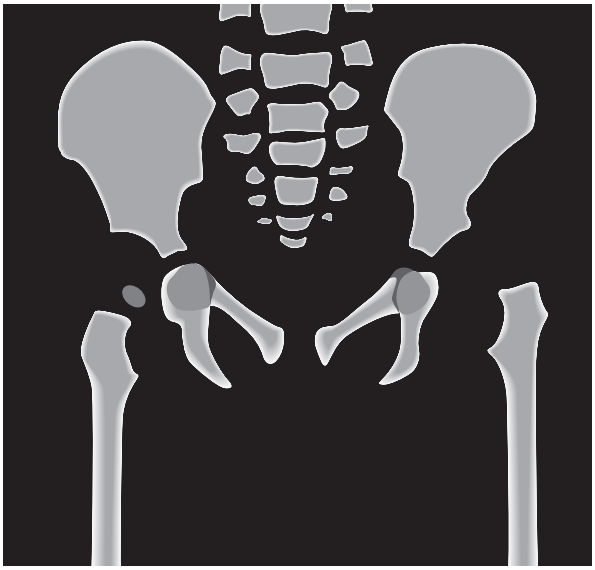

Figure 113.4. Illustration of radiographic findings associated with developmental dysplasia of the hip. The left hip is dislocated. The femur is lateral and proximal, the acetabulum is shallow and flat, and the absence of the ossific nucleus on the left is evidence of delayed ossification of the femoral head.

acetabulum and femoral head by ultrasonography measurements to establish the level of dysplasia present in infants. Another of the most commonly used classification systems for severity of persistent DDH into adulthood was developed by Crowe in the late 1970s. The Crowe classification assumes that the ratio of femoral head diameter to pelvic height is 1:5 (Table 113.1). Using this assumption, any proximal migration of the femoral head can be noted based on its relationship to 3 major landmarks identified on an AP radiograph of the pelvis: inferior margin of the acetabulum (ie, teardrop),

Table 113.1. Crowe Classification of Developmental Dysplasia of the Hip in Adults

Group	*Description*
I	Subluxation <50% or proximal dislocation <0.1% of the pelvic height
II	Subluxation 50%–75% or proximal dislocation of 0.1%–0.15% of pelvic height
III	Subluxation 75%–100% or proximal dislocation of 0.15%–0.20% of pelvic height
IV	Subluxation >100% or proximal dislocation of >0.20% of pelvic height

Reprinted with permission from Jawad MU, Scully SP. In brief: Crowe's classification. Arthroplasty in developmental dysplasia of the hip. *Clin Orthop Relat Res*. 2011;469(1):306–308.

pelvic height (ie, distance from iliac crest to ischial tuberosity); and the medial head-neck junction (ie, distance from the head-neck junction to the teardrop). The amount of migration of the femoral head is directly related to the severity of the hip dysplasia, and this amount guides both prognosis and management.

Management

The need for repeat examinations of the hips during the first year after birth cannot be overemphasized. The children with any suspected hip instability or any child with less than 60° of hip abduction should be evaluated with appropriate imaging studies and referred to an orthopedic surgeon for further evaluation. An orthopedic surgeon can aid the primary care physician in the diagnosis and management of DDH. The identification of newborns who truly require intervention is currently under debate, because only 20% of newborns with some form of hip instability require intervention and the remainder spontaneously resolve by 2 months of age.

The goal of management is to return the femoral head to its normal position within the acetabulum and restore normal hip functioning. The common practice of triple diapering should be discouraged because it is unreliable, often delays definitive therapy, and may produce complications, such as osteonecrosis of the femoral head.

The management of DDH is divided into 5 different treatment groups (Box 113.3).

The Pavlik harness is the primary method of managing DDH during infancy. This device has become the clear method of choice for treatment of infants with DDH and is accepted as the standard of treatment worldwide. The *Pavlik harness* consists of a chest strap, shoulder straps, and anterior and posterior stirrup straps that maintain the hips in flexion and abduction while restricting extension and adduction (Figure 113.5). Used properly, the harness holds the hips in a flexed and abducted position while allowing infants to move their legs within safe limits of abduction and adduction until stability is achieved. In the newborn with DDH, the harness should be worn for 23 hours a day until the clinical and radiographic examinations are normal. The harness must be worn for a minimum of 3 months by children 3 months and younger, whereas children 4 months or older usually wear the harness for a period of double their age. A newborn with a diagnosis of true dislocation must wear the harness full time until the dislocatable hip has stabilized in the acetabulum.

The harness should be applied and monitored by an orthopedic surgeon, because inappropriate application may result in adverse outcomes, such as inferior dislocation and, the most serious, osteonecrosis of the femoral head. Parents and guardians play a key role in the successful use of the harness and must be educated on the disease process and the proper use of the harness. Overall, the Pavlik harness has an 85% to 95% success rate; however, it loses efficacy as the child ages because of soft tissue contractures that manifest in previously untreated individuals.

If this treatment method is ineffective or if the diagnosis is not made until after 6 months of age, traction followed by either open or closed reduction and spica cast immobilization may be used. Closed reduction should immediately follow failure of any conservative bracing or treatment method, because good results are more difficult to obtain with increasing age, especially after a child is walking. As children age, chronic dislocation results in more permanent pathologic changes to femoral, acetabular, and soft tissue anatomy. A failure rate of approximately 10% has been reported after closed reduction, and by 2 to 3 years of age nearly 25% of patients may

Box 113.3. The Five Treatment Groups for Developmental Dysplasia of the Hip

1. Newborn to 6 months
2. Infant (6–18 months)
3. Toddler (18–36 months)
4. Child and juvenile (3–8 years)
5. Adolescent to young adult (>8 years)

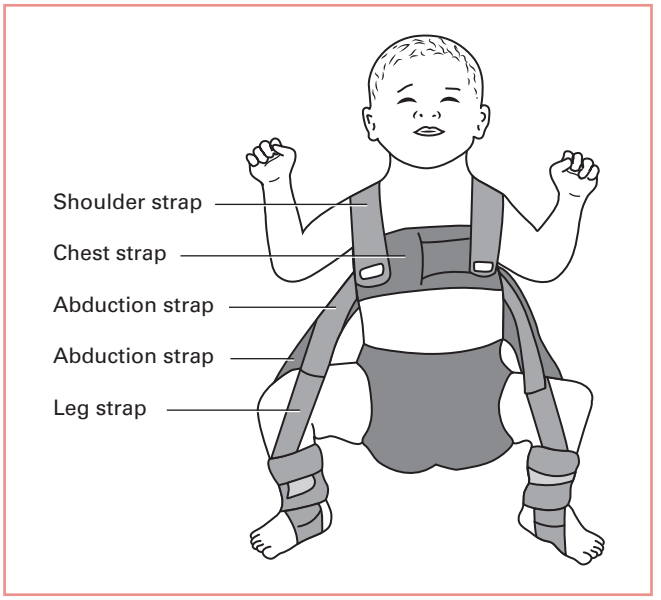

Figure 113.5. Illustration of the Pavlik harness.

develop the severe complication of osteonecrosis; thus, it is critically important to observe these children carefully for an extended period of time postoperatively. Surgical treatment is required in children older than 18 months to safely reduce the dislocated hip and to surgically re-create normal anatomy. These procedures include femoral shortening, acetabuloplasty to correct acetabular dysplasia, and *capsulorrhaphy* (ie, suturing the joint capsule).

Prognosis

The prognosis of DDH depends on age at the time of diagnosis and severity of the deformity. In children, the long-term prognosis for satisfactory hip function is good when DDH is recognized early and managed appropriately. Generally, children with DDH that is diagnosed after age 1 year have a poorer prognosis for satisfactory hip function than those with DDH that is diagnosed during infancy. The prognosis of untreated DDH differs based on the type of DDH. Generally, a patient with unilateral dislocation will have a worse prognosis than a patient with bilateral dislocation because of the associated limb-length discrepancy, asymmetric motion and strength, gait abnormalities, and subsequent degeneration of the ipsilateral knee. Although this belief is controversial, it is generally accepted that patients with chronic subluxation have the worst prognosis because of femoral point loading in the subluxated hip; this point loading results in early arthritis. Regardless of a patient's position along the spectrum of DDH, left untreated, the patient will experience disability ranging from limp to pain and stiffness of the hip as well as early onset degenerative joint disease in adult life.

CASE RESOLUTION

The infant has less than 60° of abduction of the left hip, which is a sign of DDH. An anteroposterior radiograph of the pelvis may be ordered to confirm the diagnosis. Regardless of the radiographic findings, the infant should be referred to an orthopedic surgeon for further evaluation and treatment. If hip dislocation is confirmed, the initial treatment will involve bracing with a Pavlik harness.

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CHAPTER 114

In-toeing and Out-toeing: Rotational Problems of the Lower Extremity

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CASE STUDY

A 3-year-old girl is brought to the office. Her mother is concerned because beginning a few months prior to this visit her daughter's feet appeared to "turn in" when she walked. The girl has never walked like this before, and she has no history of trauma, fever, pain, or swelling in the joints. The physical examination is within normal limits except for the in-toeing gait.

Questions

1. How can observation of a child's gait help determine the etiology of in-toeing and out-toeing (ie, rotational problems)?
2. What are the common causes of in-toeing and out-toeing?
3. Does evaluation of in-toeing and out-toeing require any laboratory or radiologic studies?
4. What is the natural history of most rotational problems?

Benign rotational variations of the lower extremities, such as in-toeing and out-toeing, occur in many healthy children. Although rotational problems that produce in-toeing and out-toeing may initially be physically alarming, spontaneous resolution occurs in most cases. Such problems are a common cause of parental or caregiver concern during infancy and childhood, but they rarely result in physical limitation. Most of these children can be managed adequately by primary care physicians and do not need orthopedic referral. A thorough understanding of the normal rotational variations that occur in children younger than 10 years of age is essential to proper treatment as well as patient and parent or caregiver education. More importantly, a general understanding is imperative to identify more serious underlying structural problems.

Specific terminology is used to describe limb positioning. *Version* is normal variation in limb rotation, whereas *torsion* refers to abnormal conditions (ie, >2 standard deviations above or below the mean). *Adduction* is movement toward the midline, whereas *abduction* is movement away from the midline. *Varus angulation* is deviation toward the midline, whereas *valgus angulation* is deviation away from the midline. An *inverted foot* is one turned toward the midline on its long axis. An *everted foot* is one turned away from the midline on its long axis.

Epidemiology

In neonates or young infants, in-toeing is most likely the result of clubfoot (ie, talipes equinovarus), isolated metatarsus adductus, or metatarsus primus varus. The prevalence of clubfoot is 1 in 1,000 live births, with a male to female ratio of 2:1. The condition is bilateral in approximately 50% of patients. Metatarsus adductus, which is much more common than clubfoot, occurs in approximately 1 in 500 live births. It is often bilateral. Internal tibial torsion is the primary cause of in-toeing in the second year after birth, and femoral torsion accounts for most cases of this condition during early childhood.

Physiologic out-toeing is classically evident in infants who have not yet begun to walk and is the most common cause of bilateral out-toeing. In older infants and children, however, lateral tibial torsion is believed to be the most common cause of out-toeing.

Clinical Presentation

Children with congenital clubfoot, metatarsus adductus, and metatarsus primus varus present with in-toeing during infancy. Typically, congenital clubfoot is evident at birth. A severe medial, midline, plantar crease is present, and the foot appears C-shaped, with both the heel and forefront turned inward (Figure 114.1). The affected foot

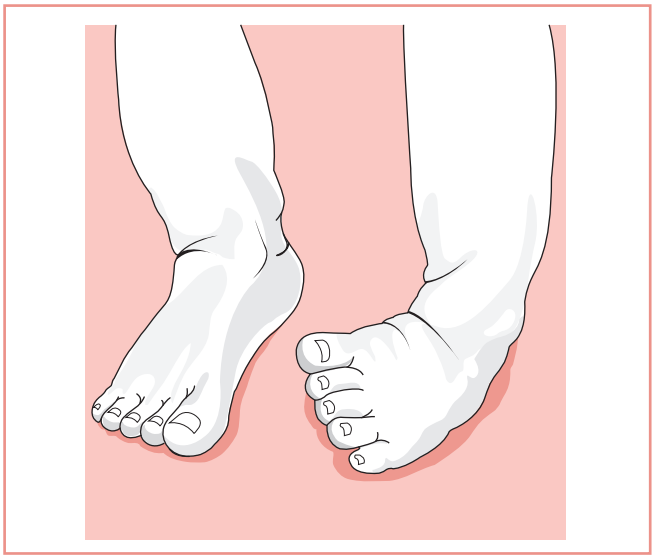

Figure 114.1. Congenital clubfoot.

is small, wide, and stiff, and the lower leg appears small because of hypoplasia of the calf muscles. In contrast to clubfoot, in metatarsus adductus and varus only the forefoot turns inward.

Tibial torsion is apparent during the second year after birth. In affected children, the feet turn inward during ambulation, but the knees are straight because the deformity is distal to the knee. Medial femoral torsion is evident at 3 to 4 years of age and usually affects girls. Affected children can sit in the "W" position with both legs behind them. As these children walk, both the knees and the feet appear to turn inward because the deformity is proximal to the knee.

Physiologic out-toeing is seen in infancy. Classically, parents or caregivers note that when they hold their child in a standing position, both feet turn outward. Approximately 5° of out-toeing is normal after age 3 years. Further degrees of out-toeing may be the result of lateral tibial torsion.

Pathophysiology

Several factors are involved in the etiology of rotational conditions. Most of these deformations are caused by intrauterine positioning. Genetics are also believed to play a role in the development of rotational problems, because parents may often have the same rotational deformity as their children. Other contributing factors include bony and neuromuscular abnormalities in clubfoot and certain sleeping and sitting positions in metatarsus adductus and medial tibial torsion. For example, sleeping in the prone position with the legs internally rotated may worsen internal tibial torsion or metatarsus adductus.

During the early intrauterine period, internal rotation of the lower extremity brings the big toe to the midline. During the later intrauterine period, infancy, and childhood, however, external rotation predominates. Alterations in this normal lateral process are caused by genetic and environmental factors, including intrauterine molding and sleep positions. Conditions influenced by intrauterine position, such as metatarsus adductus and developmental dysplasia of the hip, sometimes occur in the same child. Additionally, children with rotational deformity should undergo careful screening for other anomalies associated with intrauterine positioning as well, such as torticollis.

Typically, congenital clubfoot is an isolated birth defect and is considered idiopathic. Two major etiologies have been proposed: (1) a germline defect in the talus results in abnormal bony development, resulting in plantar flexion, inversion, soft tissue contractures, and hypoplasia of the calf muscles and the bones of the foot and (2) clubfoot represents the final common pathway of disruption anywhere along the neuromuscular unit, including the central nervous system, peripheral nerves, and muscles. Additionally, genetics are believed to play a major role because 25% of all cases are familial and there is 33% concordance of identical twins. Environmental factors, including intrauterine position and molding, are also thought to contribute.

In-toeing is usually caused by benign conditions, such as metatarsus adductus, excessive internal tibial torsion, and excessive femoral torsion. Less frequently, patients have pathologic conditions such as clubfoot, skewfoot, hip disorders, and neuromuscular diseases. Typically, out-toeing is caused by external rotation contracture of the hip, external tibial torsion, or external femoral torsion.

Conditions Associated With Rotational Variations in Children

In-toeing

Metatarsus Adductus, Metatarsus Primus Varus, and Skewfoot

Metatarsus adductus, with or without internal tibial torsion, is the most common cause of in-toeing from birth to 1 year of age. It is a functional deformity in which the forefoot is adducted with respect to the hindfoot with a neutral or slightly valgus heel. It is the most common pediatric foot problem referred to orthopedic surgeons and occurs in 1 in 500 live births and in 1 in 20 siblings of patients with metatarsus adductus. The rate is higher in males than females, twin births than singleton births, and preterm babies than term infants. Numerous theories exist as to the cause of metatarsus adductus, including in utero positioning, sleeping position of the baby, muscle imbalance, and medial cuneiform abnormality.

Presenting symptoms include cosmesis, in-toeing gait, and excessive shoe wear. On physical examination, the foot appears C-shaped with a concave medial border and convex lateral border. The forefoot can be brought into the neutral position either by stroking the lateral border of the foot or by gently straightening it. Metatarsus adductus can be classified as flexible or inflexible based on physical examination. Flexible metatarsus adductus typically resolves spontaneously and does not require splinting, bracing, or special shoes. However, the patient with rigid metatarsus adductus should undergo early casting; surgery is rarely necessary, and then only to manage resistant cases.

Congenital *metatarsus primus varus* is a bony abnormality that is characterized by an isolated adducted first metatarsal. Unlike flexible metatarsus adductus, metatarsus primus varus is a fixed deformity.

The foot cannot be brought into the neutral position, and a deep vertical skin crease is evident along the medial border of the tarsometatarsal joints. Because it is a more rigid deformity, early casting is recommended; surgery is necessary to address persistent deformity.

Skewfoot, also known as *serpentine metatarsus adductus,* is characterized by adducted metatarsals combined with a valgus deformity of the heel and plantar flexion of the talus. It is theorized that improper casting of metatarsus adductus or clubfoot may result in a skewfoot; however, most cases are idiopathic. Patients present with pain or callus formation under the head of the talus and base of the fifth metatarsal. Some feet undergo spontaneous correction, but surgery is indicated for the persistently symptomatic foot.

Dynamic Abductor Hallucis

Dynamic abductor hallucis (ie, searching toe), also known as "wandering toe" or "atavistic toe," can cause in-toeing. Children with a searching toe have a big toe that points medially when they walk. Unlike the other causes of in-toeing, which are structural and present at rest, this condition is a dynamic deformity. Searching toe results from the contraction of the abductors of the big toe during the stance phase of gait, which pulls the toe toward the midline. Typically, it resolves with age and subsequent development of fine motor coordination.

Clubfoot

Congenital clubfoot is a pathologic deformity of the foot that may be identified at birth (Figure 114.1). Clubfoot may be an isolated deformity or may occur in association with other neuromuscular anomalies, such as arthrogryposis, myelomeningocele, amniotic band syndrome, cerebral palsy, and poliomyelitis.

The diagnosis of congenital clubfoot is made at birth based on 3 conditions: forefoot varus, heel varus, and ankle equinus. Clubfoot can range in severity from a rigid deformity, in which the forefoot cannot be passively abducted into a neutral position, to nonrigid deformities, in which the forefoot can be gently brought toward the midline. Normal dorsiflexion of the ankle helps distinguish severe forms of metatarsus varus from clubfoot.

Internal Tibial Torsion

Internal tibial torsion is the most common cause of in-toeing from ages 1 to 3 years, is thought to be caused by intrauterine positioning, and is usually first noticed by parents or caregivers when their child begins to walk. Parents or caregivers often report that the child is clumsy and trips frequently. Internal tibial torsion is bilateral in two-thirds of affected children; when unilateral, the left leg is most commonly affected. Observation of gait reveals that the knees point forward but the feet turn inward. Because the knees are straight, the site of the rotational deformity lies below this joint. If the feet are normal and no metatarsus adductus or varus is present, the rotational deformity can be isolated to the lower leg. It is important to measure the thigh-foot axis and transmalleolar axis in the physical examination. Expectant observation is recommended, because the natural history of internal tibial torsion strongly favors spontaneous resolution by 4 years of age.

Internal Femoral Torsion

Internal femoral torsion is the most common cause of in-toeing in children, presenting between 3 and 6 years of age; it tends to occur in females and is usually bilateral. Typically, a child is brought to a pediatrician for evaluation after a parent or caregiver notices worsening in-toeing in a child with no history of in-toeing. Although excessive medial femoral torsion may be present at birth, it is often masked by the external rotatory forces present during infancy. Children with excessive internal femoral torsion characteristically sit with their legs in the "W" position and run with an eggbeater-type motion. Although no association has been shown between internal femoral torsion and degenerative joint disease, some studies suggest an increased association between internal femoral torsion and knee pain. This knee pain is referred to as "miserable malalignment syndrome," which results from a combination of internal femoral torsion and external tibial torsion. No treatment is necessary for most cases of femoral torsion, which usually resolves by 8 years of age.

Out-toeing

Physiologic Out-toeing

Out-toeing of infancy, which most commonly occurs in children who are just learning to walk, is caused by intrauterine positioning that results in external rotatory contractures of the soft tissues surrounding the hip. This condition may be perpetuated in children who sleep in the prone, frog-leg position, which holds the hips in external rotation and prevents normal stretching of the external rotators of the hip. Although both feet turn outward when the infant stands, the lateral rotation of both hips is normal on examination (Figure 114.2). More serious conditions, such as slipped capital femoral epiphysis, hip dysplasia, or coxa vara, are less common but should be considered.

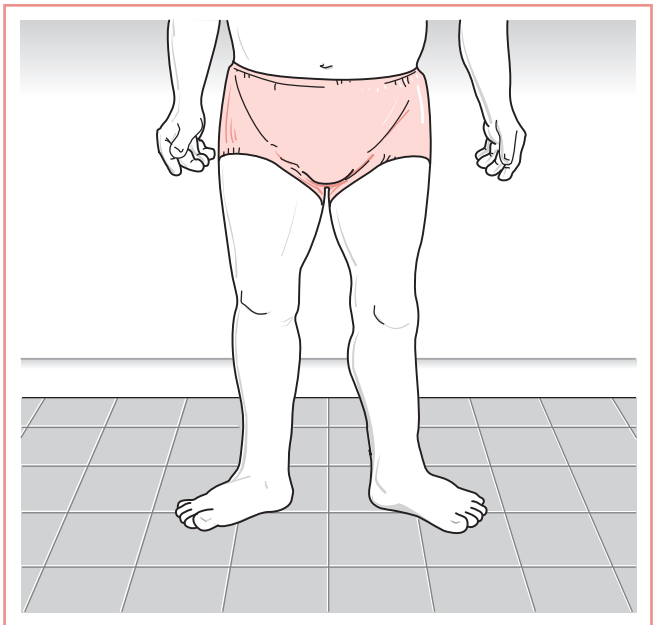

Figure 114.2. Physiologic out-toeing of infancy.

External Tibial Torsion

This condition may be suspected in children 3 to 5 years of age, but detection often is delayed until late childhood or adolescence. External tibial torsion tends to be unilateral, most often affects the right side, and generally worsens over time. Increased external tibial torsion often is associated with neuromuscular conditions, such as myelodysplasia and poliomyelitis. As the condition progresses, patients can develop disability and pain in the form of patellofemoral pain and instability. Some studies have even shown an association between external tibial torsion and degenerative joint disease of the knee.

Adolescent Hallux Valgus

Hallux valgus is well-described in the adult population but is beginning to be seen more often in the adolescent population. It is far more common in females than males, and studies have shown that up to 75% of affected patients have an affected mother. Adolescent hallux valgus is thought to be the result of a triad of deformities: abnormal bone growth, or exostosis, over the medial side of the first metatarsal head; valgus deformity of the hallux; and associated metatarsus primus varus. The etiologic factors for development of this deformity are similar to those for adults. The main contributing intrinsic factor is increased ligamentous laxity of the foot. The most common extrinsic factor is improper shoe wear. It has long been accepted that shoes with a narrow toe box, especially shoes with high heels, are strongly associated with hallux valgus. Other extrinsic factors commonly associated with hallux valgus are neuromuscular disorders, such as cerebral palsy.

The most common presenting symptom is pain over the medial aspect of the great toe metatarsal head. This is usually the result of pressure and chronic friction over the area. This pain can result in gait abnormalities and limit the patient's ability to participate in regular activity.

Differential Diagnosis

In-toeing and out-toeing may be classified according to anatomic level and usual age at presentation (Table 114.1). These conditions may be localized to 1 of 5 areas: toe, foot, tibia, femur, and hip. If in-toeing problems are placed in chronologic order by age of presentation, the affected area follows a toe-to-femur sequence.

Table 114.1. Site and Age of Onset of Rotational Problems of the Lower Extremity in Children

Rotational Variation	*Condition*	*Anatomic Site*	*Age of Onset*
In-toeing	Searching toe	Toe	Infancy
	Clubfoot	Foot	Birth
	Metatarsus adductus	Foot	Birth/infancy
	Metatarsus primus varus	Foot	Birth/infancy
	Medial tibial torsion	Tibia	Toddler stage (12–24 months)
	Medial femoral torsion	Femur	Early childhood (3–5 years)
Out-toeing	Physiologic out-toeing	Hips	Infancy
	Lateral tibial torsion	Tibia	Childhood

Evaluation

History

The clinical history must delineate the onset, duration, and progression of any structural problems. The typical natural history of benign rotational conditions is one of improvement over time, whereas a more serious condition is marked by a more progressive deformity. Relevant family and birth history, including gestational age, length of labor, complications, Apgar scores, birth weight, and length of hospital stay, should be noted. These details may heighten suspicion for cerebral palsy or the presence of hereditary disorders, such as vitamin D-resistant rickets, mucopolysaccharidoses, achondroplasia, epiphyseal dysplasia, or metaphyseal dysplasia that may affect rotational profiles. A thorough developmental history is important, because developmental delays may be a sign of underlying neuromuscular or neurologic disorders (Box 114.1). It is also important to determine whether the rotational problems cause marked functional impairment in the patient; this includes problems with tripping or pain difficulties with shoe wear.

Physical Examination

Normal variability in the lower extremities of young children must be differentiated from more serious structural problems. A detailed physical examination, including assessment of gait and neurologic and musculoskeletal function, is essential for making the correct diagnosis. This evaluation should include examination of the hips for signs of hip dysplasia, which may be associated with metatarsus adductus (see Chapter 113). Observation of the child's stature and leg-to-body ratio is also useful because short stature or disproportionate leg-to-body ratio may suggest a skeletal dysplasia.

Evaluation of postural conditions requires both static and dynamic physical examination. Static examination includes an overall evaluation of the patient and a rotational profile. The child's rotational profile, as described by Staheli, consists of

Box 114.1. What to Ask

In-toeing and Out-toeing

- Is there a family history of in-toeing or out-toeing?
- What is the birth history? Was the child a breech presentation?
- At what age did the child begin walking?
- When did the rotational deformity appear? Is it getting better or worse?
- Does the rotational problem produce any disability (eg, tripping or falling a great deal when walking or running)?
- Has any previous treatment been tried?
- In what position does the child sleep? In what position does the child sit?

5 components: internal and external hip rotation, thigh-foot axis, transmalleolar axis, heel-bisector angle, and foot progression angle during gait (Figure 114.3 and Figure 114.4).

Hip rotation in infants averages 40° of internal rotation and 70° of external rotation. By 10 years of age, internal hip rotation averages 50° and external hip rotation averages 45°. Internal rotation of between 70° and 90° is evidence of femoral torsion.

The *thigh-foot axis* consists of the rotation of the tibia and hindfoot in relation to the longitudinal axis of the thigh and indicates the degree of tibial torsion. In infants, the thigh-foot angle averages

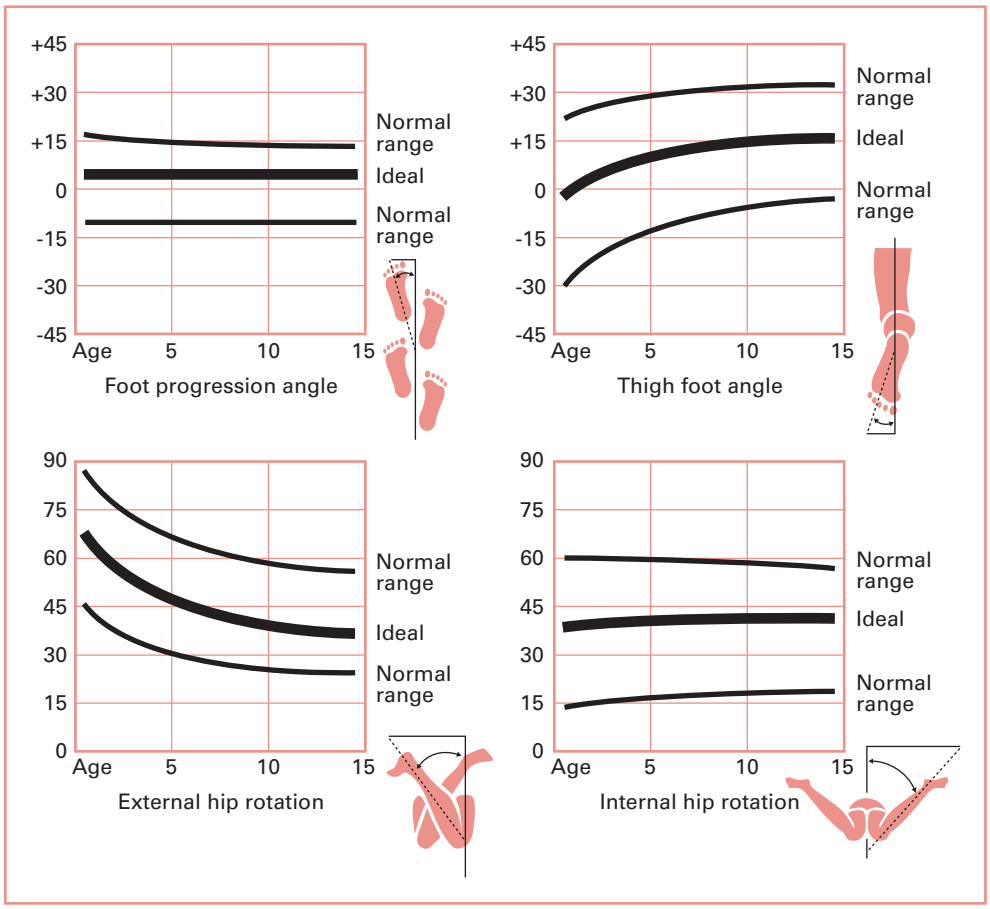

Figure 114.3. Three components of the rotational profile: foot progression angle during gait, thigh-foot angle, and external and internal hip rotation. The values along the y axis represent degrees and those on the x axis represent age in years.
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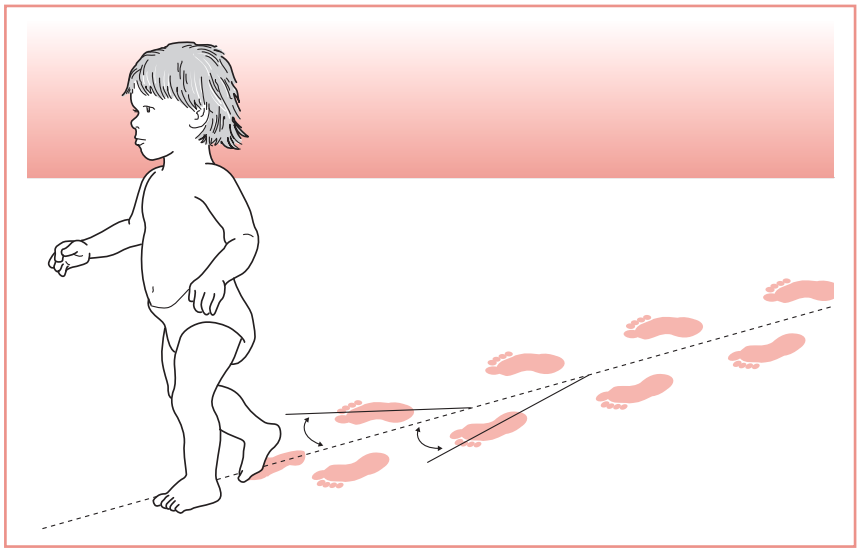

Figure 114.4. Evaluation of foot progression angle while walking.

5° internal (range: −30° to +20°). Excessive internal tibial torsion spontaneously resolves by 3 to 4 years of age, and by 8 years of age the thigh-foot axis averages 10° of external rotation.

The transmalleolar axis also aids in determining the amount of tibial torsion. It is formed by the angle at the intersection of an imaginary line from the lateral to medial malleolus and a second line from the lateral to medial femoral condyles. At gestational age 5 months, the fetus has an average of 20° of internal tibial torsion. During development, the tibia externally rotates to an average final adult position of 23° of external rotation.

The heel-bisector method is used in examination of the foot. The *heel-bisector line* is a line drawn through the midline axis of the hindfoot and forefoot. In the neutral foot, the heel-bisector line passes through the second web space.

The *foot progression angle during gait* is the angle of the foot relative to an imaginary straight line in the patient's path (Figure 114.4). Patients who in-toe are assigned a negative value, and patients who out-toe are assigned a positive value. This value represents the sum total effect of the child's structural alignment and dynamic torsion forces resulting from muscle forces.

The examination of the infant with clubfoot should include a careful examination of the back for signs of possible spinal dysraphism (eg, skin dimples and hairy patches) as well as a thorough neurologic examination.

To diagnose internal tibial torsion, the child sits at the end of the examination table with both knees flexed to 90° and the physician palpates the medial and lateral malleoli with the thumb and index finger. Normally, the medial malleolus lies anterior to the lateral malleolus (approximately 1 fingerbreadth). If the lateral malleolus is on the same plane or anterior to the medial malleolus, internal tibial torsion is indicated.

Alternatively, the diagnosis of tibial torsion can be made by measuring the thigh-foot angle (Figure 114.5). To measure the thigh-foot angle, with the child lying prone on the examination table the physician observes the relationship of the long axis of the foot compared with the axis of the thigh as viewed from above. The shape of the foot itself can also be assessed with the child in this position. Slight internal rotation is normal as children first learn to walk.

Diagnosis of medial femoral torsion can be made by observing the child's gait and measuring hip rotation. For example, when a child with medial femoral torsion ambulates, the knees and feet appear to turn inward. Internal and external hip rotation are evaluated with the child in a prone position, the pelvis flat, and the knees flexed to 90° (Figure 114.6). The degrees of normal rotation vary with age (Figure 114.3). During childhood, internal hip rotation greater than 70° is indicative of medial femoral torsion.

Imaging Studies

Routine imaging studies are not necessary for diagnosing rotational deformities. Imaging studies may be considered by the orthopedic surgeon to evaluate severe deformities in cases in which surgical correction is being considered. In the patient with clubfoot, radiography is used to assess the relationship between and development of the bones as well as to monitor cast correction.

Management

In-toeing

Metatarsus adductus generally resolves spontaneously, but stretching exercises for the foot may be advisable, particularly if the parent or guardian is anxious to "do something." Parents are instructed to manipulate the foot with each diaper change. This practice, however,

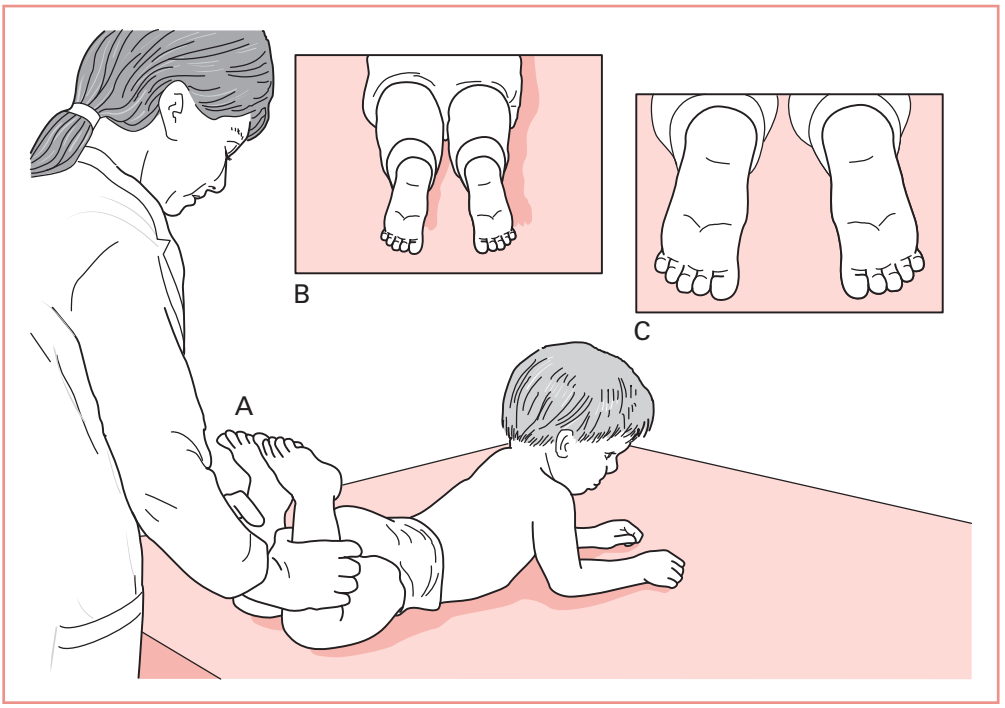

Figure 114.5. Evaluation of the thigh-foot axis. A, Observation with the child in the prone position is best. B, Determination of the thigh-foot axis. C, Assessment of the shape of the foot.

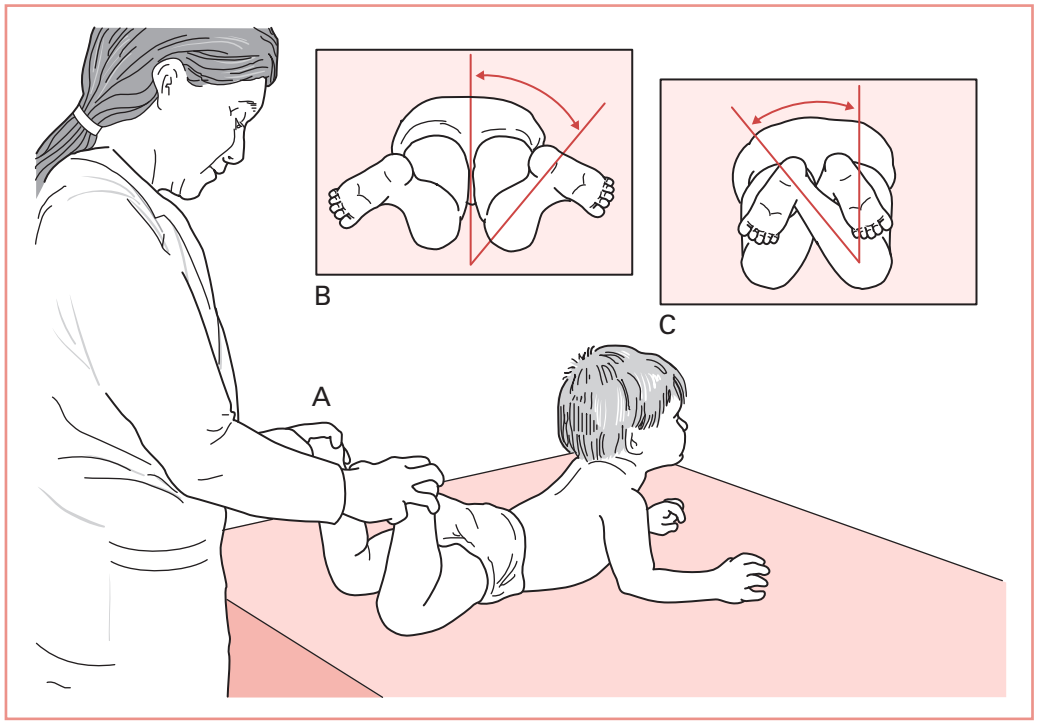

Figure 114.6. Evaluation of hip rotation. A, The child is prone, and the knees are flexed to 90°. B, Medial rotation is measured. C, Lateral rotation is measured.

should be used with discretion, because recent evidence has shown no benefit with stretching exercises when compared with no parental or caregiver intervention. Because most cases resolve within the first 3 months after birth, referral to an orthopedic surgeon should be made if the deformity persists at 3 to 4 months of age. Cast correction may be required for rigid deformities or deformities that persist beyond 3 to 4 months. Shoe modifications (eg, putting shoes on the wrong foot) should be avoided, because they have not been shown to have any long-term benefits.

Because metatarsus varus may progress when a child begins walking, referral to an orthopedic surgeon should be made as soon as the condition is detected. Serial casting followed by corrective shoes or inserts is the first line of treatment, and surgery is rarely required. Treatment for medial tibial torsion is rarely required, because this problem generally corrects with time when a child learns to walk. Night splinting, although still occasionally instituted, has not been shown to affect the natural history of this condition. If the deformity is severe, persists without improvement beyond the age of 18 months, or persists after the child has been walking for 1 year, the child should be referred to an orthopedic surgeon. Surgical correction (eg, tibial rotational osteotomy) may be required if the deformity is severe or persists beyond 8 to 10 years of age.

As with other conditions that produce in-toeing, medial femoral torsion generally does not require treatment. Even if it persists into adulthood, it usually produces no disability, nor does it increase the risk for degenerative arthritis in the involved joint. Nonsurgical treatment is ineffective. Surgical correction may be required for the patient with a history of repeated falls, severe gait problems, marked cosmetic deformity, anterior anteversion greater than 50°, or internal hip rotation greater than 80°. Derotational femoral osteotomy is the only effective method of treatment. However, it should not be performed until the child is at least 8 to 10 years of age.

Clubfoot, unlike other problems, is a pathologic deformity that requires treatment. Treatment should begin during the first week after birth and consists of serial manipulations of the foot and casting. Several months of casting may be required to attain full correction. Surgery is often required for resistant or recurrent cases. As many as 50% to 75% of patients with clubfoot may eventually require surgery. Surgery is usually delayed until an infant is 6 to 12 months of age.

Out-toeing

Physiologic out-toeing of infancy is a rotational problem that spontaneously resolves when a child learns to walk. Most cases resolve by 18 months of age. Severe lateral tibial torsion may require surgical correction with tibial derotational osteotomy.

In hallux valgus, the main concern often is cosmesis. Encouraging proper shoe wear or use of orthoses will result in improvement in the deformity; however, it can be difficult for adolescents to adhere to these recommendations. If nonsurgical treatment is unsuccessful or the patient is noncompliant, the patient should be referred to an orthopedic surgeon to discuss surgical correction.

Prognosis

Because the lower extremity rotates laterally with growth, the natural history of internal rotational problems, such as internal tibial torsion and medial femoral torsion, is one of resolution with time. In contrast, lateral tibial torsion may become worse with time.

The prognosis is excellent for most rotational problems. Parental or caregiver reassurance and education about the natural history of

these deformities may decrease anxiety and prevent unnecessary visits to specialists. Functional disability or degenerative arthritis is not commonly associated with persistence of these conditions.

Left untreated, clubfoot often results in considerable pain and disability. The affected foot can be difficult to fit with shoes. Additionally, clubfoot can be unsightly and cause children significant emotional distress.

CASE RESOLUTION

The girl seems to have medial femoral torsion because she has no history of rotational problems. Her entire leg turns in when she walks. Internal hip rotation greater than 70° confirms the diagnosis. The mother can be reassured that this is a normal, age-related phenomenon that most likely will resolve in time. The child can be reevaluated in 4 to 6 months. Orthopedic referral is not required at this time.

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CHAPTER 115

Angular Deformities of the Lower Extremity: Bowlegs and Knock-Knees

Kier Maddox Blevins, MD; Andrew K. Battenberg, MD; and Carol D. Berkowitz, MD, FAAP

CASE STUDY

During the routine health maintenance examination of a 2-year-old boy, you observe moderate to severe bilateral bowing of both legs. The child's mother reports that her son began walking at 10 months. She has not noticed problems with his gait and says he does not trip or fall excessively. On examination, the boy's weight is greater than the 95th percentile for age, but otherwise he appears to be a healthy black child.

Questions

1. What types of angular deformity affect the lower extremities in children?
2. How does age help determine whether a child has a physiologic or pathologic angular deformity?
3. What clinical measurements can help distinguish physiologic from pathologic angular deformities?
4. To what extent are radiographs used in the routine assessment of angular deformities?

With normal growth and development, the angular alignment of children's legs progresses through a series of developmental stages, from relative bowlegs to knock-knees and eventually straight legs. Rotational problems, such as in-toeing and out-toeing, are deformities in the transverse plane that occur when a bone rotates internally or externally, respectively, along its long axis (Figure 115.1). Angular deformities, such as bowlegs and knock-knees, are deformities in the frontal plane. In *bowleg deformity* (ie, *genu varum*), the lower extremity distal to the knee joint is angled or tilted toward the midline of the body (tibial varus). In contrast, in *knock-knee deformity* (ie, *genu valgum*), the lower extremity distal to the knee is tilted away from the midline of the body (Figure 115.2). Variations in the knee angle that fall outside the normal range (eg, more than ±2 standard deviations of the mean) are referred to as genu varum for bowlegs and genu valgum for knock-knees (Box 115.1). Appreciation of the normal developmental sequence in conjunction with a careful history and physical examination can help pediatricians identify pathologic cases of bowlegs and knock-knees and initiate prompt management.

Epidemiology

Bowlegs and knock-knees are common in infants and children. Although all babies are born bowlegged, parents and guardians usually do not appreciate this finding until infants begin to walk. Knock-knees occur less frequently than bowlegs, occur more often in females than males, and are commonly associated with generalized ligamentous laxity. Although the frequency of these conditions is generally unknown, a study of more than 3,000 children aged 7 through 11 years found a prevalence of 7.9% for bowlegs and 2% for knock-knees. Other literature has shown that males are up to 4 times more likely than females to have bowlegs, whereas females were 3 times as likely to have knock-knees. Weight has also been shown to be an important associated factor in prevalence of these conditions. Bowlegs are more prevalent among underweight populations than in overweight individuals. In contrast, knock-knees are more common in overweight individuals compared with individuals with normal body weight. Pathologic cases of bowlegs and knock-knees are uncommon and are defined by the degree of angulation.

Clinical Presentation

Children with bowlegs have a characteristic wide-based stance with increased distance between the knees. They may walk with a waddling gait. In-toeing may be noted as a result of associated internal tibial torsion. Evaluation for pathologic bowlegs is required in cases in which the intercondylar distance (ie, distance between the knees) is more than 10 cm with the child lying supine with the medial malleoli touching.

Severe knock-knees may produce an awkward gait with the knees rubbing. Children may walk with the feet apart in an effort to avoid

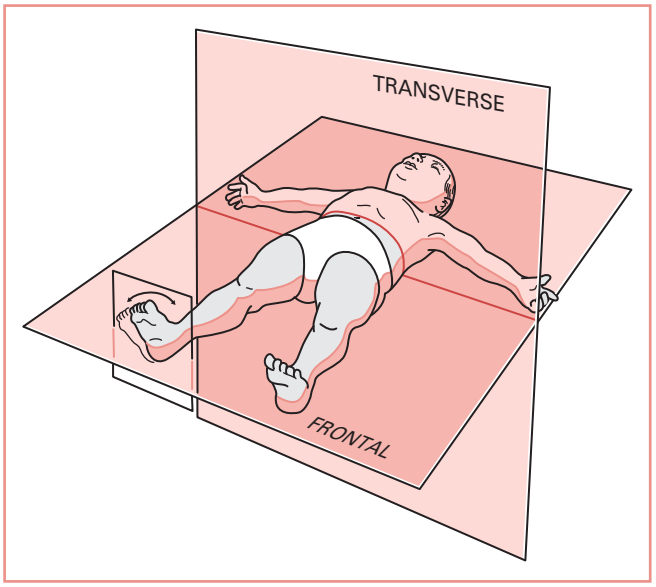

Figure 115.1. Select anatomic reference and rotational planes. Rotational problems (double-sided arrow) are deformities in the transverse plane. Angular deformities are assessed in the frontal plane.

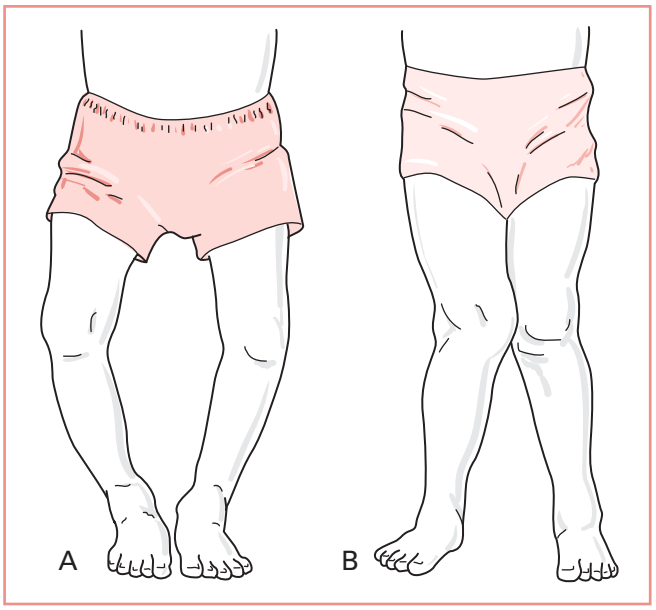

Figure 115.2. Illustration of varus (A) and valgus (B) deformities of the lower extremities. A, Bowleg deformity. B, Knock-knee deformity.

Box 115.1. Diagnosis of Pathologic Bowlegs and Knock-Knees in the Pediatric Patient

- Asymmetric deformity
- Inconsistency with the normal sequence of angular development
- Stature less than the fifth percentile for age
- Severe deformity (>10 cm intermalleolar or intercondylar distance)
- History of rapid progression
- Presence of other musculoskeletal abnormalities

knee-to-knee contact. They may need to place 1 knee behind the other to stand with both feet together. Evaluation for pathologic knock-knees is warranted in cases in which the intermalleolar distance (ie, distance between the ankles) is more than 10 cm with the child lying supine with the knees touching.

Pathophysiology

The normal variation in the angular alignment of the lower extremities changes with age. During the first 2 years of age, relative bowing of the legs is common. Although physiologic bowing of the lower leg may be appreciated at birth, it is most prominent during the second year after birth, when it most commonly involves both the tibia and the femur. In patients in whom the deformity is associated with internal tibial torsion, it may appear more striking. Physiologic knock-knees manifest between 3 and 4 years of age. The knock-knee stage resolves between 5 and 7 years of age, when normal adult alignment develops. A slight knock-knee appearance remains in normal adults. Bowlegs or knock-knees that do not follow the normal variation in angular alignment of the lower extremities require further evaluation for pathologic causes.

The *tibiofemoral angle*, that is, the angle between the long axis of the femur and the long axis of the tibia, is used to assess the angular alignment of the leg. At birth, the tibiofemoral angle is approximately 15° varus, and it decreases to 0° between ages 18 and 24 months. By age 3 to 4 years, the angle peaks at approximately 10° degrees of valgus angulation. Between 5 and 7 years of age it decreases to the normal range of approximately 7° to 9° in girls and 4° to 6° in boys (Figure 115.3).

Recent evidence has shown that weight-bearing activity may affect the alignment of lower extremity alignment at the knee in adolescent children. An association exists between normal, healthy, active adolescents who participate in weight-bearing field sports and some degree of genu varum. This small degree of bowlegs is not pathologic, although it is noted in older adolescent children who have displayed increased weekly activity levels and more years of participation in weight-bearing sports than their counterparts of the same age.

Differential Diagnosis

The most common causes of genu varum and genu valgum are presented in Box 115.2. Typically, physiologic bowlegs and knock-knees are usually bilateral, and they occur in a sequence that follows the normal developmental pattern. Lateral bowing of the tibia is commonly noted during the first year after birth. Bowleg, involving both the femur and the tibia, are pronounced during the second year after birth, and knock-knees become prominent between 3 and 4 years of age. This is the normal sequence of angular development. Typically, bowlegs is the result of normal physiologic processes, Blount disease (ie, tibia vara), or rickets. Common causes of pathologic knock-knees are severe renal rickets and a history of proximal tibia fracture.

Blount disease, a growth disturbance involving the posteromedial aspect of the proximal tibia (ie, physis, epiphysis, and metaphysis), is the most common cause of pathologic bowlegs and is the result of idiopathic undergrowth of the medial side of the tibia. The 2 forms

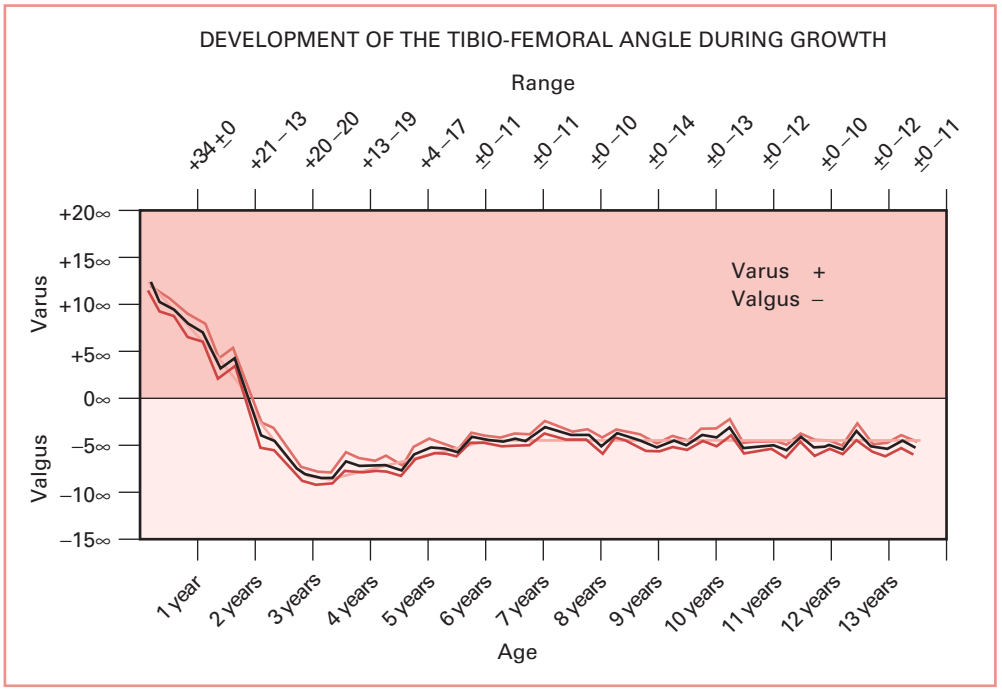

Figure 115.3. Graph showing the development of the tibiofemoral angle.
Reprinted with with permission from Salenius P, Vankka E. The development of the tibiofemoral angle in children. *J Bone Joint Surg Am.* 1975; 57(2):259–261.

Box 115.2. Common Causes of Genu Varum and Genu Valgum

Genu Varum

- Physiologic bowlegs
- Rickets resulting from vitamin D deficiency (nutritional) or vitamin D resistance (hereditary)
- Blount disease (ie, tibia vara)
- Achondroplasia
- Metaphyseal dysplasia
- Trauma, infection, or tumor of the proximal tibia (resulting in malunion or partial physeal arrest)
- Excessive prenatal fluoride ingestion

Genu Valgum

- Physiologic knock-knees
- Rickets (ie, renal osteodystrophy)
- Trauma, infection, or tumor of the distal femur or proximal tibia resulting in malunion or partial physeal arrest
- Paralytic conditions (eg, myelodysplasia, polio, cerebral palsy) resulting in contracture of the iliotibial band
- Osteogenesis imperfecta
- Rheumatoid arthritis of the knee

of the disease are early-onset (ie, infantile) and late-onset and are defined by disease development before or after 4 years of age. The late-onset form is further subdivided into juvenile (4–10 years of age) and adolescent (>10 years of age). At all ages, Blount disease is more common in black individuals than those of other ethnicities.

The infantile form of Blount disease, which initially was classified by Langenskiöld, is bilateral in 80% of patients and is associated with internal tibial torsion. The etiology is believed to involve mechanical stress on the growth plate, thus converting physiologic bowlegs to pathologic varus. Affected children often have obesity, are in the upper growth percentiles, and are early walkers, which puts early stress on the growth plate. Blount disease produces a sharp angulation at the proximal tibia, whereas physiologic bowlegs results in a gradual curvature of the legs involving both the femur and the tibia. Six stages of radiographic progression have been identified based on the degree of epiphyseal depression and metaphyseal fragmentation at the proximal tibia (ie, Langenskiöld classification). It may be difficult to distinguish between early stage Blount disease and physiologic bowlegs, although criteria have been established to help predict infantile Blount disease in children presenting with idiopathic bowlegs, that is, a body mass index greater than or equal to 22 and a tibial metaphyseal-diaphyseal angle greater than or equal to 10° degrees. These criteria have been shown to have a sensitivity of 95%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 98%.

The late-onset form of Blount disease is less common than the juvenile form and usually is unilateral. Knee pain, rather than deformity, is the most common presenting sign. It is more common in males than females, and affected children generally have obesity but are of normal height. Although the etiology is unclear, it is believed that in predisposed adolescents with obesity, repetitive trauma caused by excess weight results in decreased growth of the medial tibial physis.

Rickets, a disease of the growing skeleton, is a disorder caused by abnormal calcium and phosphorus metabolism that produces

inadequate bone mineralization. Rickets takes several forms, including vitamin D-deficient (ie, nutritional) rickets; vitamin D-resistant (ie, hereditary) rickets, which is the most common form; and severe renal osteodystrophy. Signs of rickets include short stature, poor muscle tone, joint pain, and angular deformities of the lower extremities. Nutritional rickets may occur in infants who are exclusively breastfed and do not receive vitamin D supplementation. The alignment at the time of onset of disease determines the direction of angulation. For example, vitamin D-deficient or -resistant rickets generally has an early onset and is more often associated with bowlegs. Children with rickets and bowlegs, unlike those with Blount disease, are late walkers and often have evidence of growth impairment. Renal osteodystrophy, which usually has a later onset, results in valgus deformity (ie, knock-knees).

Pathologic processes involving the proximal tibia, including trauma (eg, fractures), infection, and tumor, are additional potential causes of bowlegs and knock-knees. Overgrowth or malunion after fracture of the proximal tibial metaphysis most commonly results in genu valgum rather than genu varum.

Evaluation

History

The physician should obtain from the parents or caregivers the family history; an assessment of the child's growth and nutritional history; and a description of the deformity, its progression over time, its effect on function, and prior treatment (Box 115.3). A dietary history is also important, particularly whether the infant has been exclusively breastfed (because of the risk for vitamin D deficiency).

Physical Examination

The physical examination begins with a general screening of the child's nutritional growth and developmental status. The child's growth parameters (ie, height, weight, head circumference) should be measured and plotted on standard growth curves. Limb length should be measured bilaterally, using the distance from the anterior superior iliac spine of the pelvis to the medial malleolus of the ankle as a direct measurement of "true" leg length. The rotational status of the lower limb should be assessed, because internal tibial torsion is often associated with bowleg deformity (see Chapter 114). The child should be observed both standing and ambulating to determine the alignment of the legs in the coronal and sagittal planes. The intercondylar and intermalleolar distances can be measured with the child supine to determine the presence of excessive bowlegs or knock-knees (see the Clinical Presentation section earlier in this chapter). The intercondylar and intermalleolar distances should be measured every 6 months to monitor the progression of the deformity.

Box 115.3. What to Ask

Pathologic Bowlegs or Knock-Knees

- When was the deformity first noticed?
- Has it changed? If so, how fast?
- Has the problem been treated in any way?
- Does the problem seem to affect how the child walks?
- Has the child had any recent illness or trauma in the affected leg?
- Does anyone else in the family have a similar problem?
- Aside from this condition, is the child growing and developing normally?
- Has the infant been exclusively breastfed?
- Does the child eat a well-balanced diet?
- Does the child have any chronic medical problems, such as kidney disease?

Laboratory Tests

Most children with physiologic angulation do not require any laboratory studies. A general metabolic screening, including levels of hemoglobin, calcium, phosphorus, vitamin D, creatinine, and alkaline phosphatase, may be ordered if a systemic or metabolic abnormality is suspected.

Imaging Studies

Radiographs are usually obtained in the evaluation of bowlegs or knock-knees if pathology is suspected. True pathology is more likely if the deformity is unilateral, painful, markedly asymmetric, or progressing at an accelerated rate. If obtained, radiographs should include the entire lower extremity to allow assessment of alignment of the femur and tibia. The child should be standing, and a single weight-bearing radiograph of both legs should be obtained that includes the hip and the ankle. Radiographs centered on the knee or ankle are also helpful in determining if the physeal plate is open. Pathologic conditions such as rickets (osteoporosis, metaphyseal fraying, cortical thinning, widening of the growth plates), Blount disease (beaking of the medial metaphysis of the proximal tibia), various bone dysplasias, and forms of dwarfism can usually be ruled out by radiographs. An increased uptake of the proximal medial aspect of the tibia on bone scanning may help differentiate early infantile Blount disease from extreme physiologic bowlegs. If pathology within the joint or premature arrest of physes is suspected, computed tomography or magnetic resonance imaging can detect minor defects that may not be apparent on conventional radiographs.

Management

Angular deformities within normal developmental limits should be managed with continual observation and reassessment. The severity of the deformity should be documented, and the child should be followed at 3- to 6-month intervals until the condition resolves. Physicians should reassure parents and caregivers that bowlegs and knock-knees are normal developmental variations that resolve spontaneously with time. Generally, it is best to avoid special diets, braces or shoe wedges, arch supports, and bars, because they have not been shown to affect the normal developmental sequence.

The child with physiologic varus may be followed clinically until 18 to 24 months of age. Pathology should be suspected if correction has not begun by this time or if the angulation is progressive. The child with more than 10° of valgus or with an intermalleolar distance greater than 10 cm after 8 to 9 years of age may require further evaluation. The child with suspected pathologic bowlegs

or knock-knees should be referred to an orthopedic surgeon for further evaluation.

Although treatment of Blount disease in children younger than 3 to 4 years may consist of bracing if the deformity is mild and identified early, surgery is often necessary. Surgery involves an osteotomy to realign the tibia. Failure to do so may result in damage to the medial aspect of the knee over time. Medical management, such as administration of vitamin D for nutritional rickets, is of primary importance in the treatment of the various forms of rickets. Surgical correction, such as osteotomies to correct varus or valgus deformities, should be avoided until medical management has been maximized, because even severe deformities may resolve with conservative management.

Additionally, guided growth by the less invasive means of epiphyseal stapling (ie, hemiepiphysiodesis) can be used to restrict growth on one-half of the physis while allowing unrestricted growth on the other one-half of the physis. This results in eventual correction of the angular deformity. The ideal patient for this intervention is a child with a severe, pathologic angular deformity with open physes.

Prognosis

Physiologic bowlegs and knock-knees spontaneously resolve without further sequelae. Although knock-knees are primarily a cosmetic problem, in rare cases degenerative arthritis is a late complication. No evidence exists of a causal relationship between malalignment of the knee and the development of osteoarthritis. However, biomechanical and gait studies show an association between poor alignment in the distal lower extremity at the knee joint and the potential for osteoarthritis. Increased load occurs in the medial compartment and lateral compartment of the knee in genu varum and genu valgum, respectively. In adolescents with severe deformity, surgical correction may be necessary to prevent the acceleration of potential late complications.

CASE RESOLUTION

The boy should be evaluated for pathologic causes of genu varum, especially Blount disease, for the following reasons: his age is at the upper limit of normal for bowlegs and his deformity is severe, he is black, he has a history of early walking, and he has obesity. A standing radiograph of the lower extremities should be obtained, and the boy should be referred to an orthopedic surgeon for further evaluation and management.

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CHAPTER 116

Orthopedic Injuries and Growing Pains

Sara T. Stewart, MD, MPH, FAAP

CASE STUDY

A 6-year-old boy has a 1-week history of leg pains. He wakes up at night and cries because his legs hurt; however, during the day he is fine, with no pain and no movement limitations. He has no history of trauma, fever, or joint swelling. The family history is negative for rheumatic or collagen vascular disease. The boy's height and weight are at the 50th percentile for age, he is afebrile, and the physical examination is unremarkable.

Questions

1. What is the differential diagnosis of leg pains in school-age children?
2. What laboratory or radiographic studies are appropriate for children with leg pains?
3. How do musculoskeletal injuries in children differ from those in adults (eg, injury type, injury location)?
4. How does the physician decide the extent of the diagnostic workup in a child with extremity pain?
5. What fractures are commonly seen at different ages?

Children by nature are active and explorative. They routinely experience cuts, scrapes, minor injuries, and pain. Because primary care physicians are often the first to examine children with injuries, they play an important role in making the preliminary diagnosis and assessing the need for further evaluation and treatment. The more common complaints and injuries seen in pediatricians' offices are discussed in this chapter: growing pains, radial head subluxation (ie, nursemaid's elbow), and fractures, including growth plate injuries. Evaluation of children with limp is discussed in Chapter 118.

Epidemiology

The term "growing pains" is somewhat misleading, because no evidence exists that these pains are associated with growth. The period of middle childhood, when growing pains are diagnosed, is not the period of most rapid growth in the child. "Leg aches" or "idiopathic leg pain" may be better terms for the pains, but growing pains is the most widely used term.

The prevalence of growing pains is not well defined, but it is estimated to be between 15% and 30% of all children. These pains most commonly occur in children between 4 and 14 years of age, and girls are affected more frequently than boys.

Nursemaid's elbow, or radial head subluxation, is the most common joint injury in childhood. It occurs most commonly in children 1 to 4 years of age, with a peak incidence between 2 and 3 years of age. Other ligament and tendon injuries are relatively uncommon in prepubertal children because of the relative strength of these structures in comparison to the growth plate of the adjacent developing bone. Most commonly, fractures involving the growth plate occur before ligamentous injury. With the exception of pulled elbow, joint dislocations and ligamentous injury in children usually are the result of significant trauma.

Trauma and injury are significant causes of morbidity and mortality in childhood. Injuries are the most common reason for hospitalization in children and adolescents younger than 18 years and are the leading cause of death after age 1 year. Musculoskeletal problems account for 15% of all injuries and most commonly occur in the upper extremity. Fractures are perhaps the most common significant form of musculoskeletal injury in children who present to physicians for evaluation and treatment.

Clinical Presentation

Children with growing pains typically present with a history of intermittent, poorly localized pain in the bilateral lower extremities that occurs at night over a long period. The pain most commonly involves the calves and anterior thighs, never the joints. Symptoms usually resolve within several minutes, and in the morning the child has normal activity.

Subluxation of the radial head is characterized by a sudden onset of elbow pain associated with the traumatic event and subsequent decreased use of the arm. At the time of presentation for medical care, a child with this injury typically appears well, aside from a refusal to use the affected arm. The child typically holds the arm

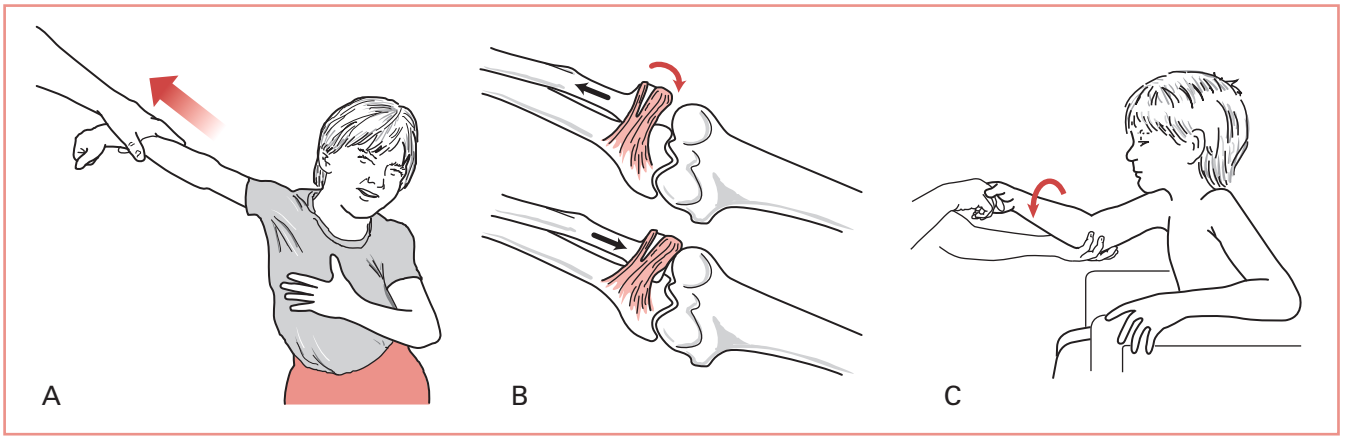

Figure 116.1. Nursemaid's elbow. The sudden traction on the outstretched arm pulls the radius distally, causing a tear in the annular ligament at its attachment to the radius. A portion of the ligament becomes trapped within the joint as the traction is released and the arm recoils. A, Mechanism of injury. B, Pathology. C, Method of reduction (ie, hyperpronation).

close to the body with the elbow in slight flexion and the forearm pronated. Usually, no gross deformity, swelling, or overlying skin trauma is evident, and the child typically refuses to supinate the forearm during examination. Point tenderness may be elicited laterally over the radial head.

Obvious deformity or lack of spontaneous movement in the extremity in question is strongly indicative of an underlying fracture. Localized swelling, tenderness, and limited range of motion all may be signs of a fracture.

Pathophysiology

Growing pains are recurrent aches or pains localized most commonly to the muscles of the legs and occasionally to the muscles of the arms of children. The pain is located deep within the extremity and not in the joints. Etiology remains unclear. Emotional and psychological stress, a low pain threshold, bone fatigue, and myalgia secondary to exercise or physical activity all have been implicated as possible contributory factors. Approximately one-third of patients also report recurrent headaches or abdominal pain.

Nursemaid's elbow is subluxation of the radial head caused by rapid and forceful extension and pronation of the forearm. This mechanism most commonly occurs when caregivers pull a child toward themselves and the child resists, wanting to go in the other direction. As illustrated in Figure 116.1, the subluxation occurs as the result of tearing of the annular ligament, with trapping of the ligament between the radius and the capitulum humeri. This injury occurs primarily in young children, because the ligamentous attachment to the bone becomes thicker with age and growth.

Because of anatomic and physiologic differences between children and adults, such as the presence of a cartilaginous growth plate, thicker periosteum, and increased plasticity of the skeleton in children, fracture patterns in children often are different from those in adults. Additionally, fractures may influence long-term growth and development of the affected limb in a growing child.

Fractures are classified based on anatomic location, type of fracture, and degree of angulation or displacement. Fracture location may be described as diaphyseal, metaphyseal, or epiphyseal/growth plate depending on the portion of the bone involved (Figures 116.2 and 116.3). Fractures may be open or closed. In closed fractures, the skin over the fracture site is intact, whereas in open fractures, the skin is broken. In cases in which 2 bone fragments are displaced relative to each other, the direction and degree of displacement are based on the distal fragment.

The Salter-Harris classification is used most commonly to classify growth plate injury (Table 116.1, Figure 116.4). Approximately 15% of all fractures in children involve the growth plate. Type 1 and 2 fractures are the most common fractures involving the growth plate. Type 3 and 4 fractures involve the epiphysis and are considered to be intra-articular. Type 5 fractures are uncommon and are caused by a crush injury to the growth plate. With type 1 and 5 fractures

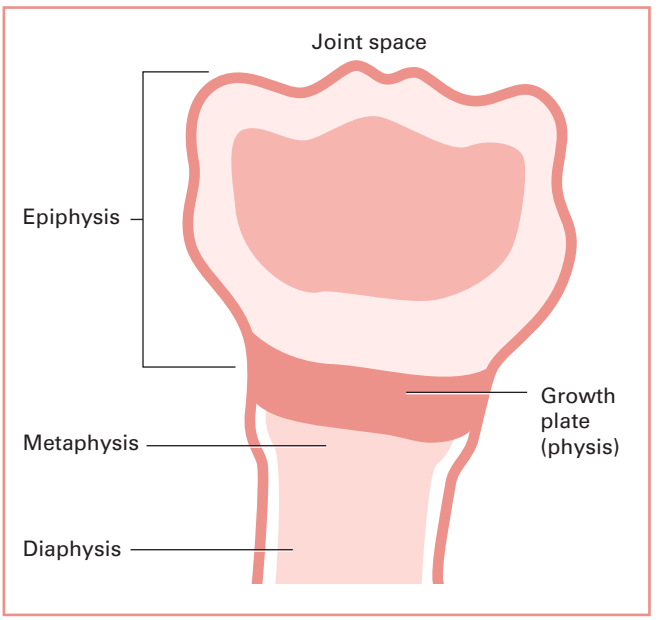

Figure 116.2. Anatomy of a long bone.

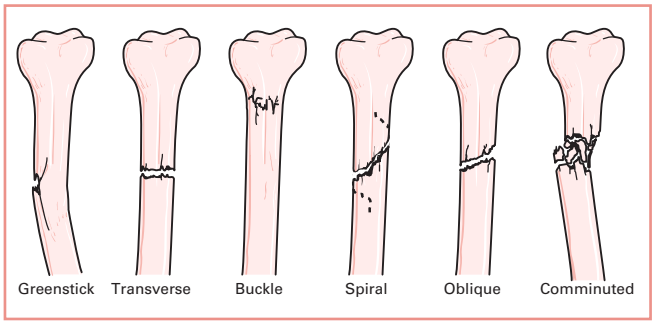

Figure 116.3. Non-epiphyseal plate fractures.

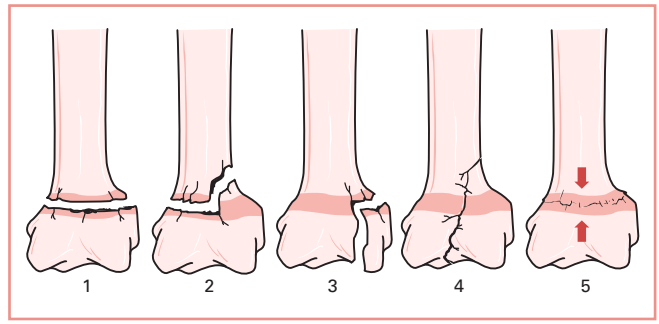

Figure 116.4. Salter-Harris classification of epiphyseal plate fractures.

Table 116.1. Long Bone Fracture Patterns That Occur in Children

Type	*Description*
	Nonepiphyseal Plate Fractures
Complete	Both sides of the bone fractured; type depends on direction of fracture line
Transverse	Perpendicular to long axis of the bone
Oblique	At an angle to long axis of the bone
Spiral	Zigzag course around the bone
Comminuted	Fractures with ≥3 fragments (rare in children)
Buckle or torus	Bone compression causes it to bend or buckle rather than break; occurs at junction of metaphysis and diaphysis
Greenstick	Cortex broken on tension side but intact on compression side
Bowing	Deformation of bone caused by bending without fracturing
Classic metaphyseal lesion	Fracture of distal, poorly mineralized metaphysis, perpendicular to long axis of bone; previously termed bucket-handle or chip fracture
	Epiphyseal Plate Fractures (Salter-Harris Classification)
Type 1	Horizontal fracture through the physis
Type 2	Fracture through the physis, extending into the metaphysis
Type 3	Fracture through the epiphysis, extending into the physis
Type 4	Fracture through the epiphysis, physis, and metaphysis
Type 5	Crush injury of the physis

Box 116.1. Common Causes of Leg Pain in Children

Growing Pains
- Leg aches
- Idiopathic leg pains

Trauma
- Fracture
- Compartment syndromes
- Soft tissue injury
- Muscle strain/sprain

Infection
- Cellulitis
- Soft tissue abscess
- Myositis
- Osteomyelitis
- Septic arthritis

Neoplasia
- Malignant bone tumors (eg, osteosarcoma, Ewing sarcoma)
- Leukemia
- Metastatic disease (eg, lymphoma, neuroblastoma)

Benign Bone Lesions
- Osteoid osteoma
- Bone cysts
- Langerhans cell histiocytosis

Collagen Disease
- Juvenile rheumatoid arthritis
- Dermatomyositis
- Fibromyalgia
- Rheumatic fever

Other Musculoskeletal Causes
- Legg-Calvé-Perthes disease
- Slipped capital femoral epiphysis
- Osgood-Schlatter disease
- Transient synovitis of the hip
- Osteochondritis dissecans
- Patellofemoral stress/chondromalacia patellae
- Generalized ligamentous laxity and joint hypermobility

Miscellaneous Causes
- Sickle cell disease pain crisis
- Psychosomatic conditions

initial radiographs may appear normal because bone fragments are not displaced. Because of involvement of the growth plate, any injury of the physis is associated with risk of growth arrest. The risk is variable, however, depending on the type of injury.

Differential Diagnosis

The diagnosis of growing pains is one of exclusion. Leg pain in children has many causes (Box 116.1). If the pain is limited to vague pains in the legs at night with no associated limp or signs of inflammation, the differential diagnosis may be limited to growing pains, restless legs syndrome, general systemic diseases (eg, leukemia), benign bone tumors (eg, osteoid osteoma), or possibly fibromyalgia.

Leukemic infiltration of the bones may cause leg pain before systemic signs such as fever, weight loss, and adenopathy are present. Osteoid osteoma, a benign bone tumor that most commonly occurs in adolescent boys, characteristically causes pain that is worse at night and is usually relieved by nonsteroidal anti-inflammatory medications. Unlike with growing pains, however, the pain may be localized to 1 place. Fibromyalgia likely is underdiagnosed in the pediatric population; in adults, this condition is a well-recognized cause of chronic, generalized limb pain without a clear, organic source. It occurs more commonly in adolescents than in younger children. This benign, intermittent musculoskeletal pain syndrome is associated with multiple tender "trigger points," stiffness, fatigue, and a nonrestorative sleep pattern.

When evaluating for nursemaid's elbow, an elbow fracture should be ruled out. Certain fractures and specific features of fractures deserve mention (Figure 116.3). Fractures that often occur during childhood include clavicular fracture, which is the most common childhood fracture and most commonly fractured bone from birth trauma, and spiral fractures of the distal tibia, that is, the "toddler's fracture" or childhood accidental spiral tibial fracture. This fracture typically occurs in children who have not been walking long, such as those between 9 months and 3 years of age. It is thought to be caused by a rotational force on the lower leg, which could occur as an ambulatory child falls in a twisting motion. Often, when the child presents for medical care, the parents or guardians are unaware of a history of trauma and the chief symptom is that the child refuses to bear weight on the affected leg. Elbow fractures, including supracondylar humerus fractures as well as lateral and medial condyle fractures, commonly occur as the result of a fall directly on the elbow or on an outstretched hand. These fractures require careful attention to neurovascular status because of the risk of associated injury to the median or radial nerve or brachial artery, which could result in Volkmann contracture. A *Monteggia fracture* is a dislocation of the radial head in association with an ulnar shaft fracture. Long bone fractures in preambulatory children, rib fractures, classic metaphyseal lesions, and the presence of multiple fractures in a child are all concerning for nonaccidental trauma and should prompt a more thorough evaluation of possible physical abuse (see Chapter 144).

Because of the relative weakness of the physis compared with the surrounding ligaments, trauma sustained near joints may be more likely to cause a type 1 Salter-Harris growth plate fracture rather than ligamentous injury (eg, sprain, strain). Therefore, it is important to include this type of fracture in the differential diagnosis of children with point tenderness near the end of a long bone because this injury requires cast immobilization.

Box 116.2. What to Ask

Growing Pains

- When (ie, what time of day) does the pain typically occur?
- How long has the pain been occurring?
- Does the pain resolve and then recur in any predictable manner?
- Where is the pain? Does it change location?
- Does anything make the pain better or worse?
- Is the child sick in any other way?
- Does the pain interfere with the child's activities or with sleep?
- Does the parent notice any changes, such as swelling or redness in the child's legs?

Orthopedic Injuries

- How did the injury occur?
- How long ago was the injury sustained? When did the symptoms begin?
- Was the incident witnessed by an adult?
- How strong was the injuring force? From what direction did it come?
- What was the position of the affected extremity at the time of the injury?
- Did the child experience any head trauma or loss of consciousness?
- What, if any, first aid was administered at the scene?
- Has the child been able to move the affected extremity since the injury occurred?

Evaluation

Accurate diagnosis of orthopedic injuries in pediatric patients often is challenging, because children may be not only poor "historians" but also uncooperative with examinations, especially if they are experiencing pain.

History

A thorough history is essential for the accurate diagnosis of growing pains and orthopedic injuries (Box 116.2). A complete history of the events related to the injury should be obtained, including what happened after the injury was sustained.

Physical Examination

The physical examination of the child with suspected growing pains should include evaluation for signs of systemic disease, such as fever, lymphadenopathy, hepatosplenomegaly, abnormal growth, and generalized weakness or fatigue. Leg length and circumference should be measured. The legs should be palpated and range of motion assessed in the hip, knee, and ankle. Gait should be assessed as well.

The child with suspected nursemaid's elbow should be observed for how the child holds the affected arm compared with the unaffected arm. The child should be evaluated for limited active motion at the elbow and resistance to attempts at passive movement, especially supination. No swelling should be present, but tenderness over the radial head may be elicited. Additionally, the shoulder and wrist should be thoroughly examined.

It is important to perform a complete physical examination in the presence of the parent, guardian, or other chaperone after first having the child disrobe. Examining only the involved extremity is insufficient. The presence of a deformity, point tenderness, or limitation of motion supports the diagnosis of a fracture. All long bones should be palpated, and the presence of bruises and scars should be noted, because these may indicate child abuse. Examination of the involved extremity includes inspection of the overlying skin for swelling, lacerations, or punctures. The degree of active and passive motion and strength compared with the uninvolved side should be noted. In cases of suspected leg injuries, the child's gait should be observed, if possible. Assessment of neurovascular function distal to the injury includes evaluation of capillary refill, peripheral pulses, and motor and sensory function.

Laboratory Tests

A complete blood cell count and erythrocyte sedimentation rate may be considered for the child with leg pains that do not resolve or for the child with symptoms that are atypical for growing pains.

Rheumatologic screening tests can be ordered based on abnormal findings (eg, elevated erythrocyte sedimentation rate, elevated white blood cell count). A diagnosis of growing pains requires normal results on all laboratory tests. Routine laboratory studies are not necessary in the evaluation of nursemaid's elbow or fractures. Because femoral fractures often are associated with significant blood loss, however, it is important to monitor hematocrit in these patients.

Imaging Studies

If leg pains persist and interfere with routine activity, radiography or bone scanning of the legs may be considered. Radiographic evaluation is not required for the child with nursemaid's elbow if presentation is typical and reduction is successful. Radiographs, if obtained, usually are negative because often the dislocation is corrected during positioning for the x-ray itself. Radiographs should be obtained in children with suspected fractures, however. Fractures involving the growth plate, especially Salter-Harris type 1 and 5 fractures, may be particularly difficult to diagnose radiographically because the growth plate is primarily cartilaginous and, thus, radiolucent. Bone scanning or follow-up radiography may be done to diagnose suspected fractures when initial radiographs are negative.

Management

Parental/guardian education and reassurance about the benign nature of growing pains are important. The pains themselves usually respond to supportive measures, such as heat, massage, and analgesia. Stretching exercises for the legs also have been recommended. Referral to an orthopedic surgeon should be considered if the pain is severe and persistent and a specific diagnosis cannot be made based on physical examination and laboratory workup.

Subluxation of the radial head is among the few medical conditions with a dramatic, immediate cure. To manage the elbow, the annular ligament must be reduced back to its anatomic position. In both common methods of reduction, the elbow is stabilized with application of pressure laterally over the radial head with the thumb of the medical professional. The first method involves rapid, firm hyperpronation of the forearm. In the second method, the forearm is firmly supinated, after which the elbow is flexed. Although success rates are high with both methods of reduction, several studies suggest superiority of the hyperpronation method. A click may be heard or felt as the radial head is reduced, and pain relief usually is immediate for children who are treated shortly after their injury. Return of function may require up to 30 minutes, however. If treatment is delayed, such rapid relief of symptoms may not occur. After reduction, the parent or guardian should be advised that the child may need mild pain medication. Some physicians recommend short-term immobilization in a sling or splint to facilitate soft tissue healing. If reduction is unsuccessful, the physician should consider obtaining radiographs and referring the patient for orthopedic consultation.

Most fractures should be referred to an orthopedic surgeon for evaluation and management unless the primary care physician is experienced in reducing and casting fractures. Several techniques are used in fracture management. Closed reduction is the nonsurgical reduction or realignment of fracture fragments. Open reduction implies that an incision has been made to expose the fracture and proceed with manipulating the bone fragments into place. Fixation, or stabilization of the fracture with any type of device, may be required following the reduction. *Internal fixation* is that in which the device is placed under the skin, and *external fixation* is that in which the device begins outside the skin but passes through the skin to bone. Indications for open reduction include failure of closed reduction, the necessity for precise anatomic reduction, and complex multisystem trauma.

Certain fractures are common in pediatrics. Most clavicular fractures do not require reduction and can be managed with immobilization in a sling for 4 to 8 weeks. Elbow fractures (eg, lateral condyle fracture, supracondylar humeral fracture) are at particular risk for neurovascular compromise and often necessitate open reduction to achieve anatomic reduction. Typically, distal forearm fractures are managed with closed reduction and casting; however, forearm fractures in the middle and proximal thirds of the bone may be more difficult to reduce in the office setting. Stable metacarpal and phalangeal fractures can be splinted in an aluminum splint or taped to an adjacent finger (ie, buddy taping). The metacarpophalangeal joints should be maintained in 50° to 90° of flexion, and the interphalangeal joints should be maintained in approximately 20° of flexion to minimize stiffness. Unstable finger fractures may require open reduction and pin fixation.

Femoral shaft fractures in infants and children can be managed with closed reduction and spica casting. As the child ages, a fixation device may be required in addition to the closed reduction. Open reduction is rarely necessary. Closed reduction and cast immobilization usually are used in the management of tibial shaft fractures. Short cast immobilization may be required for metatarsal fractures, and buddy taping is used for stable toe fractures.

Because of the potential for infection, open fractures are orthopedic emergencies that require immediate attention and orthopedic consultation. Careful wound débridement is required. Antibiotics should be administered, and tetanus immunization may be given based on a review of the immunization history.

Prognosis

Growing pains resolve over time without sequelae. Recurrence of nursemaid's elbow is common, occurring again in up to one-third of patients. Thus, parents and guardians should be cautioned about pulling a child's arms or lifting a child by 1 hand. Remodeling is the spontaneous correction of deformity. Fractures in children generally heal faster and remodel better than equivalent fractures in adults. Vascular and nerve injuries and growth disturbances are potential complications of fracture and fracture management. Compartment syndrome, a potentially serious vascular injury, may also occur.

Growth plate injuries require special attention because of the potential for subsequent growth abnormalities of the affected bone. Prognosis of growth plate fractures depends on the type of injury sustained. Generally, Salter-Harris type 1 and 2 fractures are associated with a good prognosis for long-term healing and growth. The severity of injury and accuracy of reduction determine the prognosis

of type 3 and 4 fractures. Growth arrest is common after type 5 fractures because the physis itself is injured.

CASE RESOLUTION

The child has the benign condition commonly referred to as growing pains. Management involves parental education and reassurance. Local heat, massage, and analgesia (ie, ibuprofen) may be recommended.

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CHAPTER 117

Sports-Related Acute Injuries

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CASE STUDY

A 15-year-old female basketball player reports 6 months of intermittent pain in her left knee. Occasionally the knee gives out while she is playing ball. The patient denies any associated swelling or erythema over the joint. She can walk with no problem and reports no history of direct trauma to the area. She is otherwise healthy.

Physical examination shows the patient to be a well-developed, well-nourished adolescent girl in no acute distress. The examination is normal, with the exception of mild pain to direct palpation of the left patella. No swelling, erythema, or effusion of the knee joint is evident, and full range of motion is noted in the left hip, knee, and ankle. The back is straight.

Question

1. What are some of the most common orthopedic findings in adolescent patients, and why do they occur in this age group?
2. What is the pathophysiology of overuse syndromes?
3. What is the purpose of the preparticipation physical evaluation?
4. What criteria help determine if an adolescent should be disqualified from participation in a competitive sport?
5. What are the current recommendations for the management and rehabilitation of acute soft tissue injuries?

Many adolescents with varying degrees of athletic ability participate in sports during their middle school/junior high school and high school years. Some participate in sports at the college level as well. Regardless of the reason for participating, team sports are an important means by which children and adolescents can experience both winning and losing. Individuals learn the importance of group participation and develop interactive skills with other team members. They are exposed to the concept of physical fitness, which can improve body image as well as self-esteem.

Participation in athletics carries significant risks, however. Injuries, inappropriate coaching, and aggressive training sessions are not uncommon occurrences that may have long-term sequelae for young athletes. Primary care physicians are responsible not only for the evaluation of children prior to their participation in sports but also for the prevention, diagnosis, and management of athletic injuries.

Epidemiology

Recent estimates indicate that approximately 38 million young athletes participate in organized sports in the United States each year. Of these, 4 million athletes younger than age 14 years and 2 million high school–age athletes are treated for a sports injury. These numbers have increased dramatically in the past 20 years. This increase is thought to be multifactorial, including an increase in the number of female athletes in the United States following the passage of Title IX of the Education Amendments of 1972, a new emphasis on year-round competition, single-sport focus, and increased training intensity. Several studies have attempted to quantify the overall injury rate associated with athletic participation. In general, the rate of injury for individuals 13 through 19 years of age is 7% to 11%. Approximately 20% of those injured sustain a significant injury. For boys, the sports with the highest injury rate in all age groups are football, basketball, and soccer. In girls, gymnastics, cheerleading, and roller skating account for the most injuries. Sex-related differences have been found in some studies, depending on the sport. Overall, boys tend to have more shoulder-related injuries, whereas girls tend to have more knee and ankle injuries as well as more problems with overuse syndromes. Reports indicate that the severity of sports-related injuries increases with age. Along with the increased incidence of injuries, sports-related injuries previously thought to be rare in the pediatric population are on the rise. For example, anterior cruciate ligament (ACL) ruptures are occurring with increased frequency in this demographic, especially among high school–age females. Management of such injuries is complicated in skeletally immature individuals because of the need to preserve growth potential.

Preparticipation Physical Evaluation

The goal of the preparticipation physical evaluation (PPE) is to identify any physical conditions or abnormalities that may predispose the young athlete to injury. Examples include a history of concussion with head trauma or an incompletely healed sprain.

The PPE consists of 2 parts: a review of the patient's current health and medical history, including sports injuries and family history relating to participation in strenuous exercise, and a complete physical examination with a focus on the musculoskeletal system.

Known as a "2-minute orthopedic examination," the musculoskeletal examination is a detailed assessment of all muscle groups, assessing their strength, tone, and function. Congenital or acquired deformities should also be noted. The American Academy of Pediatrics has developed a form specifically for the PPE visit (see Chapter 38).

Disqualification from participation in specific sports is appropriate in certain situations. Competitive sports are classified according to their degree of contact or impact and their strenuousness. Recommendations differ depending on the adolescent's medical condition and the type of sport the athlete desires to play. For details of these recommendations, see Selected References at the end of this chapter. Fortunately, many young athletes are healthy and rarely need to be restricted from sports participation.

Clinical Presentation

Older children and adolescents with sports-related injuries usually present with specific reports of pain or swelling in a particular joint (Box 117.1). Additionally, they may report nonspecific musculoskeletal pain occurring in certain areas, such as the lower back or shoulder, or they may report a limp, decreased range of motion of an extremity, or an inability to participate in a desired activity without pain.

Pathophysiology

Unlike adults, adolescents are particularly susceptible to injury because their bones and joints are not fully mature. Most injuries that occur during adolescence involve the epiphysis, which is the weakest point of the musculoskeletal system. Additionally, the presence of congenital anomalies, such as leg length discrepancy and hip rotation abnormalities, puts the young athlete at further risk for injury. Biomechanical and neuromuscular factors, hormonal influences, and anatomic differences have also been proposed as reasons for higher rates of some injuries in young female athletes compared with young male athletes. For example, patellofemoral pain syndrome, which presents as knee pain exacerbated by activity, is a common problem in adolescent females, affecting nearly 1 in 10 of those who are active. Contributing biomechanical factors include tight iliotibial bands, weak gluteal strength, and a relative genu valgum resulting from increased hip width in female individuals. This combination causes valgus stresses at the knee, internal femoral rotation, and abnormal patellar tracking, which places the athlete at increased risk for patellofemoral syndrome.

Most orthopedic injuries are the result of either macrotrauma or microtrauma. Sprains are an example of macrotrauma, whereas overuse syndromes can be considered microtrauma. *Macrotrauma* is the result of complete or partial tearing of muscle, ligaments, or tendons and often is associated with acute injuries. In contrast, *microtrauma* usually is caused by chronic repetitive trauma to a particular area, resulting in inflammation and ultimately, pain. Such injury most commonly occurs in soft tissues, such as muscle and tendon, but can occur in bone as well.

Box 117.1. Diagnosis of Orthopedic Injury in the Older Child or Adolescent Patient

- Joint pain or swelling
- Tenderness to palpation of the affected joint
- Decreased range of motion of the affected joint or extremity
- May or may not have associated bruising of the skin overlying the injury

Definitions

A *sprain* is a stretching injury of a ligament or the connective tissue that attaches bone to bone. A *strain* is a stretching injury of a muscle or its tendon, which is the connective tissue that attaches muscle to bone. *Tendinitis* is an inflammation of the tendon. *Apophysitis* is an inflammation of the apophysis, which is the site of ligamentous or tendinous attachment to growth cartilage (eg, Osgood-Schlatter disease [ie, apophysitis of the tibial tubercle], Sever disease [ie, calcaneal apophysitis]). A *stress fracture* is an incomplete fracture often occurring in the bones of the legs and feet from repetitive trauma to the area. It is believed that the pain associated with shin splints may result in part from atypical stress fractures of the distal tibia.

Overuse syndromes occur from repetitive microtrauma to the musculoskeletal system secondary to excessive or biomechanically incorrect activity. Typically, they are the result of training errors in which athletes are "trying to do too much too fast." Common syndromes in adolescents include Osgood-Schlatter disease, shin splints (ie, medial tibial stress syndrome), and patellofemoral syndrome (ie, chondromalacia patellae).

Grading of Sports Injuries

Sprains most commonly occur in the knee or ankle, and they can be classified according to the degree of injury. Assigning a grade that describes the injury is useful when considering the prognosis of a particular injury. Grading an injury is helpful when referring patients to sports medicine specialists (eg, orthopedists). Typically, sprains are classified as grade I, II, or III (Table 117.1). Grade I generally refers to stretching of the ligament, grade II is a partial tear of the ligament, and grade III is a complete tear of the ligament. Joint stability, range of motion, and degree of pain and swelling determine the grade of the sprain. The grading system for strains, however, is based on an assessment of strength. Because strains typically do not cause joint instability, criteria for grading strains are different from those for sprains and may be more subjective (Table 117.2).

Table 117.1. General Classification of Sprains

Grade	Joint	Range of Motion	Weight Bearing	Pain	Swelling
I	Stable	Normal	Normal	+	+
II	Stable	↓	↓	++	++
III	Unstable	↓↓	↓↓	+++	+++

Abbreviations: ↓, reduced; ↓↓, markedly reduced; +, mild; ++, moderate; +++, severe.

Table 117.2. General Classification of Strains

Grade	Strength	Palpable Defect	Pain
I	>4	–	+
II	3–4	±	++
III	<3	±	+++

Abbreviations: –, none; ±, variable; +, mild; ++, moderate; +++, severe.

Differential Diagnosis

The differential diagnosis of orthopedic conditions depends on the anatomic site of the injury or symptom and the mechanism of injury. Box 117.2 lists some of the more common orthopedic conditions by location. Anomalies of skeletal development, such as congenital angular deformities of long bones, and soft tissue abnormalities, such as Ehlers-Danlos syndrome, should be considered as possible etiologies for overuse syndromes. Other nonorthopedic conditions, such as collagen vascular diseases, infections, and tumors, may present with joint or bone symptomatology.

Evaluation

History

The history should focus on the musculoskeletal system and the mechanism of injury (Box 117.3). Other pertinent information about the activity level and competition level of the sport should be ascertained as well, because it can help the physician determine any underlying factors that may have precipitated the injury, such as a chronic overuse mechanism. It is also important to note the increased numbers of children engaging in early single-sport specialization, because these children may be prone to overuse injury and should be evaluated for signs of burnout.

Box 117.2. Differential Diagnosis Based on the Site of Injury

Back
- Epiphyseal injury
- Herniated disk
- Muscle strain
- Spondylolysis

Upper Extremity
- Acromioclavicular sprain
- Acute elbow injury
- Finger injury
- Flexor-pronator tendinitis
- Glenohumeral dislocation
- Glenohumeral subluxation
- Hamate fracture
- Impingement syndrome
- Lateral epicondylitis
- Olecranon bursitis
- Scaphoid fracture
- Sternoclavicular sprain
- Wrist sprain

Lower Extremity
- Achilles tendinitis
- Ankle sprain
- Anterior cruciate ligament sprain
- Calcaneal apophysitis
- Femoral stress fracture
- Iliac apophysitis
- Iliac crest contusion
- Medial/lateral ligament sprain
- Osgood-Schlatter disease
- Patellar dislocation/subluxation
- Patellar tendinitis
- Patellofemoral stress syndrome
- Plantar fasciitis
- Posterior cruciate ligament sprain
- Prepatellar bursitis
- Quadriceps contusion
- Shin splint syndrome

Box 117.3. What to Ask

Sports-Related Injuries
- What is the acuity of the injury?
- What activity or sport was the patient engaged in at the time of the injury?
- How often has the patient engaged in this sport or particular activity in the past?
- Were there any new additions to the routine in this instance?
- Did the pain begin after a single injury or after repetitive activity?
- If the injury is related to a repetitive activity, does the pain occur at a specific time during this activity?
- What was the mechanism of injury?
- Is the pain incapacitating?
- Has a similar injury ever occurred in the past?
- How was the injury treated?
- Was there any pain following the previous injury?
- Does the patient feel as if he or she has completely recovered?
- How was this current injury managed acutely?
- Has the patient altered daily activity in any way to compensate for this problem?

Physical Examination

The physical examination should focus on the musculoskeletal system. Any adolescent who has not undergone a physical examination within the past year, however, should first undergo a complete physical examination to exclude any systemic condition that might manifest initially as musculoskeletal pain. This is especially important in adolescents with chronic or systemic symptoms, such as intermittent extremity pain, swelling of an affected joint, and fever.

Any pain or swelling of an affected joint or muscle should be noted. In the patient with a history of acute trauma, an area of ecchymosis or joint effusion may be seen. The affected joint should be tested for range of motion and joint laxity to determine the degree of sprain. Special testing for ligamentous laxity should be performed (Figure 117.1). For the knee, the most common methods are the anterior drawer test and the posterior drawer test to evaluate anterior and posterior movement of the knee joint, respectively. However, the Lachman test has gained considerable popularity because it has been shown to be a more sensitive and specific test for ACL injury. The patient is examined in a supine position on an examining table, and the knee, ligaments, and tibia are assessed. It is important to note that in the setting of a recent injury, soft tissue swelling and guarding because of pain can limit the efficacy of these tests. Additionally, a large knee effusion is evidence of significant intra-articular pathology, such as a fracture or ligament rupture.

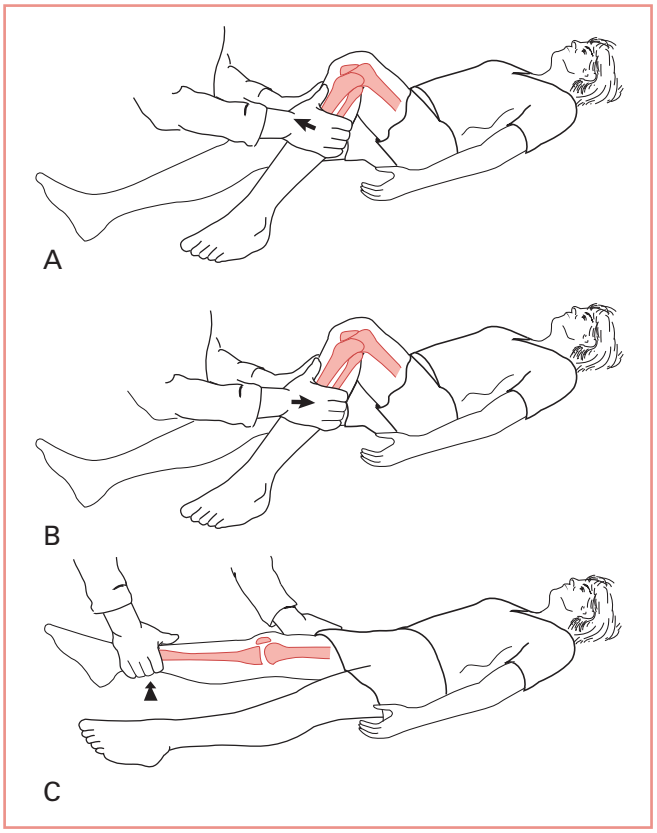

Figure 117.1. Maneuvers used to determine stability of the knee joint. A, Anterior drawer test, in which anterior force is applied (arrow). B, Posterior drawer test, in which posterior force is applied (arrow). C, Medial ligament stability, in which lateral force is applied (arrow).

Muscle spasms and diminished range of motion in an adjacent joint should be noted because these may be signs of a strain injury. Strength of the strained muscle or muscles should be assessed, and any pain with palpation or range of motion should be noted. A palpable defect of the muscle is suggestive of complete rupture of the muscle, whereas muscular contusions are associated with localized pain, soft tissue swelling, or hematoma. Pinpoint tenderness over a particular bone may be indicative of a fracture or, if the tenderness is elicited at the site of a tendon insertion, inflammation. Reviewing the mechanism of injury and the timing of the symptoms often is helpful in differentiating between a fracture and tendinitis.

Laboratory Tests

A complete blood cell count and erythrocyte sedimentation rate may be helpful in adolescents with a history of chronic joint pain or swelling. If the results are abnormal, further workup is indicated to distinguish between a collagen vascular disease (eg, systemic lupus erythematosus), an infection (eg, osteomyelitis), or, rarely, an arthritic disorder (eg, juvenile idiopathic arthritis). In adolescent populations, in which individuals may be sexually active, the physician should consider the possibility of gonococcal arthritis.

Imaging Studies

Often, a plain radiograph of the involved joint or bone is the only necessary diagnostic study. Because ankle sprain is such a common occurrence, it is important to understand when a radiograph is necessary to rule out fracture. The Ottawa Ankle Rules are guidelines for obtaining radiographs in acute ankle injury; they are approximately 100% sensitive and have been validated for use in children older than 6 years (Box 117.4). Plain radiographs of joints above and below the symptomatic area are also sometimes indicated. For example, the Maisonneuve fracture, which is a fracture of the proximal fibula near the knee that can occur with serious ankle injury, can be missed if a knee radiograph is not obtained in addition to ankle views. Advanced diagnostic tests, such as computed tomography, have limited value in the evaluation of an acute soft tissue injury. Magnetic resonance imaging may be indicated for injuries that do not improve despite adequate treatment and rehabilitation. See Chapter 118 for a discussion of imaging studies used to evaluate a child presenting with limp.

Management

With soft tissue injuries, the aim of acute management is to limit the extent of bleeding and inflammation that occur in the first 48 to 72 hours after injury. The mnemonic RICE (rest, ice, compression, elevation) is helpful. Rest should be explained as "relative rest," because the athletes should be allowed to do as they wish as long as they are pain-free during or within 24 hours of the activity. Ice should be placed in a plastic bag and applied directly to the skin for a continuous 20 minutes. Longer periods of icing are discouraged because this can result in peripheral nerve palsy caused by cryoinjury. Patients should ice the injury 3 to 4 times a day for the first 48 hours, after which icing should be done at least once daily until the swelling or pain is gone. Compression is especially important and should be started as quickly as possible after injury. When applying compression bandages, wrapping should begin distal to the injury and should proceed proximally; this prevents trapping of edema and swelling distal to the compression wrap, allowing proper drainage of injured tissue. The injured extremity

Box 117.4. Ottawa Ankle Rules

- Obtain an ankle radiograph if ANY of the following:
  - — Bone tenderness at the posterior edge or tip of the lateral malleolus
  - — Bone tenderness at the posterior edge or tip of the medial malleolus
  - — Bone tenderness along the distal 6 cm of the tibia or fibula
  - — Inability to bear weight both immediately after injury AND in the emergency department for 4 steps
- Obtain a foot radiograph if ANY of the following:
  - — Bone tenderness at the base of the fifth metatarsal
  - — Bone tenderness at the navicular bone
  - — Inability to bear weight both immediately after injury AND in the emergency department for 4 steps

should be elevated as often as possible. The use of this plan for soft tissue injuries facilitates early healing and allows rehabilitation to proceed more quickly.

Anti-inflammatory or analgesic medications, such as ibuprofen, aspirin, and naproxen, are useful in controlling pain and swelling. For adolescent patients, dosages are similar to those used in adults: aspirin, 650 to 1,000 mg every 6 hours; ibuprofen, 400 to 800 mg every 6 to 8 hours; or naproxen, 500 mg twice daily. To minimize gastrointestinal side effects, the medication should be administered with a snack or milk. Ideally, these drugs should be used for 7 to 10 days. Neither oral nor parenteral corticosteroids are indicated in the management of overuse injuries or acute trauma to the extremities.

After the acute phase, therapy is aimed at rehabilitation and resolution of any edema or hematoma (Box 117.5). Athletes should slowly begin range-of-motion exercises as tolerated. Although complete tissue healing may take 6 to 8 weeks, most young athletes may return to athletic activity sooner.

Depending on the degree of tissue damage, modified activity should be recommended initially in athletes who have suffered from overuse syndromes. Complete rest is rarely indicated. Participation in another sport, such as swimming or cycling, often is preferable to complete immobilization. In addition to the use of anti-inflammatory agents, physical therapy is another important therapeutic modality. Cryotherapy, whirlpool baths, or alternating heat and ice treatments can be helpful. Reconditioning should be continued after 3 to 12 weeks of modified activity, depending on the extent of recovery. This entails gradual strengthening and flexibility training as well as reevaluation of previous modes of training to minimize the risk of reinjury (Box 117.6). Additional aspects to consider are strength imbalances and biomechanics, such as those that occur in patellofemoral syndrome. By identifying specific musculoskeletal imbalances, the physician can suggest stretches and strengthening exercises specific to the patient's deficits.

Some sports injuries may require surgical management because of severe trauma to key anatomic structures requiring ligamentous repair or fracture fixation. Tibial spine fractures, ACL reconstruction, and other injuries necessitating hardware, such as osteochondritis dissecans, may result in malunion, deformity, and arthrofibrosis in skeletally immature patients. The closer adolescent patients are to skeletal maturity, the lesser their risk for such sequelae. Orthopedic surgeons and pediatricians must effectively communicate management plans and options to patients and parents or guardians of patients with these injuries so they are prepared for the outcomes and associated complications that may arise.

Box 117.5. Principles of Rehabilitation Following Sports-Related Injury

- Resolution of hematoma
- Resolution of edema
- Regain full range of motion or flexibility
- Regain full muscle strength and endurance
- Regain agility and coordination
- Regain cardiovascular endurance

Box 117.6. Rehabilitation of Musculoskeletal Injuries: The Four Phases[a]

- Limit additional injury and control pain and swelling (RICE mnemonic).
- Improve strength and flexibility (ie, range of motion) of the injured structures.
- Progressively improve strength, flexibility, proprioception, and endurance training until near-normal function is attained.
- Return to exercise and sports symptom free.

Abbreviation: RICE, rest, ice, compression, elevation.

[a] Modified from Hergenroeder AC. Prevention of sports injuries. *Pediatrics.* 1998;101(6):1057–1063.

Prevention

Injury prevention is an important aspect of sports medicine with which the primary physician should be familiar. One element of injury prevention is the recognition of risk factors associated with sports injuries. In general, risk factors can be divided into 2 subgroups: nonmodifiable and modifiable. Nonmodifiable risk factors include sex, individual physical features, and the type of sport. Modifiable risk factors include flexibility, alignment, strength, endurance, and proprioception. Additionally, exercise preparation, hydration, and adequate warm-up are important in preventing injury. According to research, stretching before exercise may help reduce the risk of muscle strain regardless whether the stretching is dynamic or static.

Because many injuries are the result of "trying to do too much too soon," proper physical training and conditioning are essential, no matter how fit the athlete appears. Stretching, warm-up and cool-down exercises, and the type of equipment used for the sport should be reviewed with the athlete during the sports physical visit. The type of sport to be played should be reviewed as well and, if participating in a contact sport, the adolescent should be matched with other athletes based on weight and pubertal development rather than age. Some studies suggest that such matching greatly reduces the risk of injury to the smaller, less mature athlete. Because an old or incompletely healed injury is a significant risk factor for reinjury, the athlete should receive proper treatment and rehabilitation of all previous injuries before returning to play. Protective equipment, especially for collision and contact sports, as well as for sports involving a ball or racquet, also should be emphasized to athletes and their parents or guardians.

The National Strength and Conditioning Association advises that under correct supervision, strength and resistance training in both children and adolescents can have numerous health benefits when age-appropriate guidelines are stringently followed. Benefits include enhanced strength and endurance, resulting in fewer injuries and improved bone health. Strength training should not be

confused with competitive weight lifting, which involves the use of maximum loads and shear forces that may hinder growth and damage skeletal structure and development in active youth. The American Academy of Pediatrics recommendation for avoiding weight training and advanced resistance training until Tanner stage 5 of pubertal development should be followed in most cases, particularly those in which adequate supervision and expertise is unavailable. The risk of overuse injuries and overtraining should be discussed with the patient and parents or guardians. Education about the hazards of anabolic steroid use and creatine also may be indicated.

Prognosis

Orthopedic injuries in young athletes and active adolescents have a great capacity for healing if given the opportunity. Early medical intervention to prevent irreversible tissue damage ensures complete recovery in most cases. Long-term sequelae are associated with repeat trauma, incomplete treatment, and chronic inflammatory changes. Some conditions, however, such as Osgood-Schlatter disease, resolve even without treatment and do not result in permanent joint damage.

CASE RESOLUTION

The teenager has symptoms and physical findings consistent with patellofemoral pain syndrome, which is traditionally referred to as chondromalacia of the patella. Because plain radiographs are rarely helpful in confirming the diagnosis, none are necessary at this time. Management should include strength training for the quadriceps muscles, activity modification, nonsteroidal anti-inflammatory drugs, and ice compresses after activity.

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CHAPTER 118

Evaluation of Limp

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CASE STUDY

A 6-year-old boy with a 2-day history of right knee pain and limp is brought to the office. He has no history of knee trauma, swelling, redness, or associated fever. The medical history is unremarkable. The boy is afebrile, and his height and weight are at the 10th percentile for age. Examination of the right leg reveals decreased abduction and internal rotation of the hip; the knee is normal. The boy limps when he walks and favors his right leg.

Questions

1. What is the differential diagnosis of painful and painless limp in children?
2. What is the differential diagnosis of knee pain in children?
3. What laboratory tests and radiographic studies are indicated in the evaluation of children with limp?
4. What is the appropriate treatment of the child with a suspected infectious cause of limp?

A *limp* is a gait disturbance that occurs when an effort is made to minimize weight bearing on an affected leg to reduce pain and instability. The disturbance may be secondary to muscle weakness, deformity, pain, or a combination thereof. Muscle weakness may be caused by primary muscle disease, neurologic conditions, or disuse atrophy. Structural causes of limp include leg length discrepancy and joint stiffness, whereas painful causes of limp include trauma; synovitis; infection of bone, joint, or soft tissue; or neoplasm. A limp may be a sign of significant underlying disease, and accurate diagnosis and appropriate management are essential to prevent potentially serious morbidity.

Epidemiology

A patient may limp because of pain originating in a leg or because of pain referred from the abdomen or spine. Age often defines the diagnostic possibilities; certain disorders are more common among particular age groups. Infectious causes of limp occur more frequently in infants and young children, and noninfectious causes are more common in school-age children and adolescents (Table 118.1).

Clinical Presentation

Painful limp typically has an acute onset and may be associated with systemic signs, such as fever, especially when the etiology is infectious. The toddler may simply refuse to walk or walk with a slow, cautious gait when in pain rather than limp. Painless limp often has an insidious onset and is commonly caused by weakness (eg, muscular dystrophy) or deformity (eg, leg length discrepancy).

Pathophysiology

Normal gait has 2 phases: stance and swing. During the stance phase, both feet are on the ground as 1 heel strikes while the opposite foot moves to pre-swing; during the swing phase, 1 foot is not touching the ground as the limb is moved forward. Stance phase is shortened in limp to decrease the amount of time spent bearing weight on the affected side or to minimize instability.

Normal adult gait is smooth and efficient, requiring the coordinated actions of the muscles of the legs and pelvis. Normal gait in children varies according to age and developmental maturity. The toddler typically walks with a broad-based, tiptoe, "bouncing" gait with the arms abducted for balance. A toddler may initiate the stance phase with either toe or heel strike. By 2 years of age, a child should initiate the stance phase consistently with heel strike. At 3 to 4 years of age, a child should exhibit normal adult gait with reciprocating arm swing most of the time.

Several types of abnormal gait are recognized. An *antalgic gait* has a characteristic shortened stance phase resulting from pain. *Trendelenburg gait* is caused by weakness of the hip abductors (eg, gluteus medius muscle) in which the pelvis dips down during stance phase, producing a swaying type gait. A tiptoe gait or toe-to-heel gait is normal in children for several months after they learn to walk. Persistence of such a gait beyond 2 years of age is abnormal, however, and may result from idiopathic heel cord contracture or contracture secondary to cerebral palsy.

Differential Diagnosis

Trauma is a frequent cause of limp in children and adolescents. In toddlers, a fall may not be witnessed, and they may present with limp or refusal to walk because of an occult fracture, such as toddler fracture (Figure 118.1). *Toddler fracture* is an oblique or spiral fracture of the middle or distal tibia that occurs after a fall or jump involving a twisting motion. Toddlers are at risk for such injuries because of their unsteady gait. Tpyically, standard anteroposterior (AP) and lateral radiographic views are obtained to determine if a fracture is present. The radiographic appearance may initially be normal, and

Table 118.1. Differential Diagnosis of Limp in Children

Limp Type	*1–3 Years of Age*	*4–10 Years of Age*	*≥11 Years of Age*
Painful	Septic arthritis/osteomyelitis Transient synovitis Intervertebral diskitis JIA Neoplasia (ie, leukemia, metastatic disease) Trauma (ie, toddler fracture) Child abuse	Septic arthritis/osteomyelitis Transient synovitis Trauma LCPD (acute phase) Intervertebral diskitis JIA Sickle cell pain crisis Lyme arthritis Neoplasia (ie, leukemia, primary bone tumor, metastatic disease)	Trauma Septic arthritis/osteomyelitis SCFE Osgood-Schlatter disease JIA Sickle cell pain crisis Lyme arthritis Neoplasia (ie, leukemia, primary bone tumor, metastatic disease)
Painless	DDH Neuromuscular disease (ie, cerebral palsy) Leg length discrepancy	LCPD (chronic phase) DDH Neuromuscular disease (ie, cerebral palsy, muscular dystrophy) Leg length discrepancy	SCFE Leg length discrepancy Neuromuscular disease (ie, cerebral palsy, muscular dystrophy) Scoliosis

Abbreviations: DDH, developmental dysplasia of the hip; JIA, juvenile idiopathic arthritis; LCPD, Legg-Calvé-Perthes disease; SCFE, slipped capital femoral epiphysis.

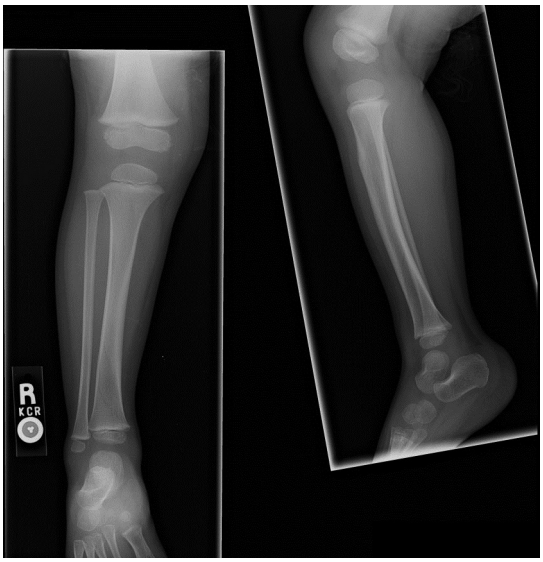

Figure 118.1. Anteroposterior (left) and lateral (right) radiographs of toddler fracture evidenced by elevation of the periosteum.
Courtesy of Michael Diament, MD.

oblique views may be helpful in visualizing the fracture. Follow-up radiographs or bone scanning may be necessary to make the diagnosis. The older child usually can recall a specific injury and localize pain to a specific area. In the patient with tenderness over an open growth plate, a splint should be applied and the patient should be closely followed even if radiographs appear normal because of the possibility for a Salter-Harris type I fracture, which occurs through the growth plate and may not be evident radiographically.

Painless limp in the toddler may be the result of developmental dysplasia of the hip, cerebral palsy, or leg length discrepancy (ie, anisomelia). As a result of developmental dysplasia of the hip, a child may have a Trendelenburg gait secondary to leg length discrepancy or to weakness of the hip abductors. Children with spastic cerebral palsy often walk on their toes because of increased tone or heel cord contracture. Functional or apparent leg length discrepancies may be the result of pelvic obliquity or spinal deformity. Children with true leg length inequality compensate by walking on tiptoe on the shorter side or bending the knee on the longer side. Limb discrepancies may be managed with orthoses (eg, heel lifts) for mild cases, whereas surgical lengthening or shortening procedures may be necessary for more severe cases.

Transient synovitis of the hip is a benign, self-limited inflammatory process involving the synovial lining and is among the most common causes of limp in the young child. The exact cause of the inflammation is not known. Although an association has been noted with certain upper respiratory infections, no infectious agent has been identified. Compared with the general population, children who were subsequently diagnosed with Legg-Calvé-Perthes disease (LCPD) have been noted to have a higher incidence of transient synovitis. This may be related to misdiagnosis or the historical use of traction to manage transient synovitis. Age of onset varies, but transient synovitis typically affects children 4 to 10 years of age, although it can present in younger or older persons. Males are affected at approximately twice the rate as females. Individuals usually present with acute onset of unilateral hip pain associated with a limp. A patient may experience referred pain to the anterior thigh or knee. Associated systemic symptoms, such as fever, are rare or absent and should prompt an investigation for another cause. A child may hold the leg in a position of abduction, flexion, and external rotation to reduce intracapsular pressure and associated pain. Symptoms are usually unilateral, but fewer than 10% of patients have bilateral involvement, often with 1 side more symptomatic than the other.

Transient synovitis is a diagnosis of exclusion and must be differentiated from more concerning diagnoses, such as septic arthritis. Consequently, laboratory evaluation typically consists of complete blood cell count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Usually, the results are within normal limits or are slightly elevated. Radiographs are often obtained, which usually are normal or show signs suggestive of an effusion. Ultrasonography often is performed to evaluate for the presence of an effusion within the joint, which may occur with this condition. If arthrocentesis is performed, the fluid in transient synovitis usually has a white blood cell (WBC) count of less than 50,000/mm^3 and a negative Gram stain. Individuals with normal laboratory values or with a fluid aspirate that is not suggestive of septic arthritis (when arthrocentesis has been performed) typically are managed with supportive care and close follow-up within 24 to 48 hours. Rest and nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstays of therapy. Nearly all children recover within 3 to 10 days with no significant sequelae. Recurrence rates can be as high as 69% within the first year of an episode of synovitis.

Septic arthritis occurs as the result of infection within the joint space. In children, this usually occurs in the setting of bacteremia, with hematogenous spread to the highly vascular synovial membrane. It can also occur from contiguous spread of an adjacent infection (eg, osteomyelitis) or by direct inoculation (eg, surgery, penetrating trauma). *Staphylococcus aureus* remains the most common pathogen identified across all age groups, with increasing incidences of community-acquired methicillin-resistant strains. Infants younger than 2 months also can be infected by neonatal pathogens, such as *Streptococcus agalactiae* (eg, group B streptococcus) and gram-negative enteric organisms (eg, *Escherichia coli*). Septic joints in children between 2 months and 5 years of age are usually caused by *S aureus, Streptococcus pyogenes, Streptococcus pneumoniae,* and *Kingella kingae*. Children older than 5 years usually have infections caused by *S aureus* or *S pyogenes. Neisseria gonorrhoeae* infections may be seen in sexually active adolescents. Historically, *Haemophilus influenzae* type b (Hib) was a common pathogen of osteoarticular infections in children; however, its incidence dropped dramatically after the introduction of the Hib vaccine.

Infants and children with septic arthritis often present with fever, decreased use of the affected extremity, limp, or refusal to walk. The most commonly affected joint is the hip, which is classically held in a position of abduction, flexion, and external rotation to reduce intracapsular pressure and associated pain. Passive range of motion typically elicits significant discomfort and resistance. Parents or caregivers of infants may notice increased crying with manipulation of the legs with activities such as diaper changing.

Subtle or early cases of septic arthritis often present a diagnostic challenge because of the potential for considerable clinical and laboratory overlap with transient synovitis. Unfortunately, no highly sensitive or specific laboratory test exists that can readily distinguish these 2 entities. Temperature higher than 38.5°C (101.3°F) was shown to be the single best predictor of septic arthritis in 1 study, with no children diagnosed with transient synovitis having a temperature above 38.5°C (101.3°F). Other predictors include refusal to bear weight, ESR greater than 40 mm/hour, a CRP greater than 2.0 mg/dL, and serum WBC count greater than 12,000/mm^3. The presence of 1 of these 5 factors was associated with a probability of approximately 37% for having septic arthritis, whereas the presence of all 5 factors was associated with a probability of 98% for the condition. Imaging often consists of plain radiography and ultrasonography. Radiographs usually are nondiagnostic but may demonstrate joint space widening suggestive of an effusion. Ultrasonography usually demonstrates the presence of an effusion.

Analysis of synovial fluid remains the standard for the diagnosis of septic arthritis, and arthrocentesis of any effusion under sedation or anesthesia is indicated if a clinical suspicion of septic arthritis exists. A WBC count greater than 50,000/mm^3 within the fluid aspirate generally is considered diagnostic for septic arthritis; however, elevated counts also occur with certain rheumatologic conditions. Regardless of WBC count, the presence of bacteria on Gram stain of joint aspirate is suggestive of infection. Routine cultures of joint aspirate as well as peripheral blood cultures should be obtained. Additionally, with the increasing recognition of *K kingae* as a causative agent in septic arthritis in young children, joint aspirations should be directly inoculated into blood culture bottles to enhance isolation because this organism is difficult to recover with standard culture techniques. In most studies, only approximately 50% of joint aspirate cultures grew out an identifiable pathogen. In 1 study, close to 50% of the aspirates that were sterile on standard culture media grew out *K kingae* from blood cultures. Other studies suggest sending a polymerase chain reaction assay, which is better for detecting *K kingae*, or a nasopharyngeal and throat culture, given this is often an area of colonization for patients with *K kingae* infection.

Joint damage from the purulent effusion can occur within 6 to 8 hours, which is why emergent evaluation and treatment is necessary. Complications occur in 10% to 25% of all cases of septic arthritis of the hip, and that rate increases in cases in which 5 days or more have passed before initiation of therapy. These complications include abnormal bone growth, permanent limp, unstable articulation of the affected joint, and decreased range of motion.

Osteomyelitis is an infection of the bone that typically is caused by a bacterial organism. Nearly 50% of pediatric cases of osteomyelitis occur in children younger than 5 years. Most cases of osteomyelitis in children occur from hematogenous deposition of bacteria into the bone marrow during a transient episode of bacteremia. Other cases may be the result of contiguous spread of an adjacent infection or direct inoculation. Osteomyelitis most commonly begins in the highly vascularized metaphysis of long bones of young children. The femur, tibia, and pelvis account for most cases. As with septic arthritis, *S aureus* remains the most common organism identified across all age groups, with an increasing incidence of methicillin-resistant *S aureus* (MRSA). Other organisms include *S pyogenes, S pneumoniae,* and *K kingae.* Young infants can also be infected by neonatal pathogens, such as group B streptococcus and enteric gram-negative organisms. Individuals with sickle cell disease (SCD) are at increased risk for infection with

Salmonella. *Haemophilus influenzae* type b should also be considered in unvaccinated children.

Children often present with pain or localized symptoms at the affected site. More than one-half have a fever. Younger children may present with limp, reduced range of motion, or refusal to bear weight. In the setting of subperiosteal spread, erythema, warmth, and swelling may be evident at the affected site.

Laboratory tests can be supportive of a diagnosis of osteomyelitis but usually are not specific. Typically, a CBC, ESR, and CRP are obtained along with blood cultures. Leukocytosis may be present, but in more than one-half of cases, the WBC count is normal. Inflammatory markers are elevated in up to 90% of patients. A CRP greater than 10 mg/L (1.0 mg/dL) may also increase the suspicion for osteomyelitis complicated by septic arthritis. Blood cultures are positive in 40% to 55% of patients. Because of the importance of discerning the causative organism, the physician should consider ordering polymerase chain reaction assays for *K kingae* given its increasing incidence and difficulty to isolate. Radiographs are often normal or show only soft tissue changes early in the course of the disease. Periosteal reactions and lytic lesions rarely present before 10 to 21 days into the disease course. Bone scanning can be helpful in the preverbal child or in individuals who cannot localize their pain. Magnetic resonance (MR) imaging has become the study of choice, with a reported sensitivity of 97%. It is quite useful for distinguishing between bone and soft tissue infections.

Diskitis refers to an inflammatory process involving the intervertebral disks. This disease typically occurs in children younger than 5 years. It occurs almost exclusively in the lumbar region, causing progressive limp, back pain, and refusal to walk. Most children with the condition are afebrile. Diskitis is thought to occur in younger children because of the presence of vascular channels in the cartilaginous region of the disk space as well as abundant intraosseous arterial anastomoses. These vascular channels disappear with age. Laboratory studies are often nonspecific, with slight elevations in the peripheral WBC count and ESR. Radiographs are abnormal in 75% of patients, with decreased vertebral disk space and erosion of adjacent vertebral end plates being the most common abnormalities seen. Bone scanning demonstrates nonspecific increased marker uptake in the affected area. Computed tomography (CT) rarely provides a specific diagnosis and is not generally used. Magnetic resonance imaging demonstrates characteristic inflammatory changes and allows for differentiation from other conditions, such as vertebral osteomyelitis.

The exact etiology of diskitis is not known, and the treatment is somewhat controversial. Several authors propose that diskitis is the result of an infectious process and warrants antibiotic therapy. Others propose that it is simply a benign self-limited inflammatory disease because most cultures are sterile and patients can recover without any antimicrobial therapy. In most cases, broad-spectrum antibiotics and strategies to prevent kyphosis are initiated.

Legg-Calvé-Perthes disease is an idiopathic avascular necrosis of the femoral head. The exact etiology is unclear but involves some disruption in the vascular supply of the capital femoral epiphysis. The disease most commonly occurs in children 3 to 12 years of age (median age, 7 years), and it is 4 to 5 times as common in boys as in girls. The condition is bilateral in up to 15% of cases. Children typically present with a chronic intermittent limp that can be painful or painless. It is not uncommon for the child to be symptomatic for months before a diagnosis is made. Pain is usually worsened with internal rotation and abduction.

Laboratory tests are usually normal. Radiographs early in the course of the disease may be negative or show widening of the joint space. In later stages, radiographic findings include increased density and decreased size of the femoral head (ie, necrosis), patchy areas of radiolucency near the epiphysis (ie, fragmentation), and flattening of the femoral head (ie, reconstitution; Figure 118.2).

Slipped capital femoral epiphysis (SCFE) is a displacement or slipping of the femoral epiphysis from the neck of the femur through the open physis (ie, growth plate). This is the most common hip disorder affecting adolescents. It is more common in boys than girls and occurs more frequently among blacks and Hispanics than non-Hispanic whites. Typical age of onset is 9 to 16 years. Individuals often have overweight and frequently present with a chief symptom of knee pain. They often have an antalgic gait. The foot is externally rotated in severe slips but may be neutral or pigeon-toed in mild slips. Examination of the knee is normal without discomfort, despite the report of knee pain. Passive flexion of the hip often results in obligate external rotation. Typically, pain is elicited on internal rotation. With stable SCFE, the individual can walk with or without crutches; with unstable SCFE, walking is not possible. Laboratory testing is not indicated. Anteroposterior and batrachian (ie, frog-leg) radiographs of the hip are diagnostic in approximately 80% of patients. Early radiographic findings include widening of the physis, whereas slippage is noted radiographically later in the disease process (Figure 118.3). Imaging assessment of both hips is important because SCFE is bilateral in up to 20% of patients. When done by an experienced technician, ultrasonography has been shown to be an effective diagnostic tool, with a sensitivity of 95%. A slip can be visualized on CT or MR imaging; however, MR imaging is much more sensitive and can detect physeal widening in the pre-slip condition.

Osgood-Schlatter disease (OSD), or traction apophysitis of the tibial tubercle, is an overuse injury of the knee that occurs most commonly

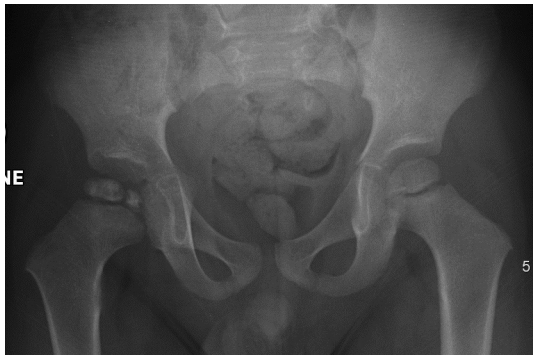

Figure 118.2. Anteroposterior pelvic radiograph of a patient with Legg-Calvé-Perthes disease.
Courtesy of Michael Diament, MD.

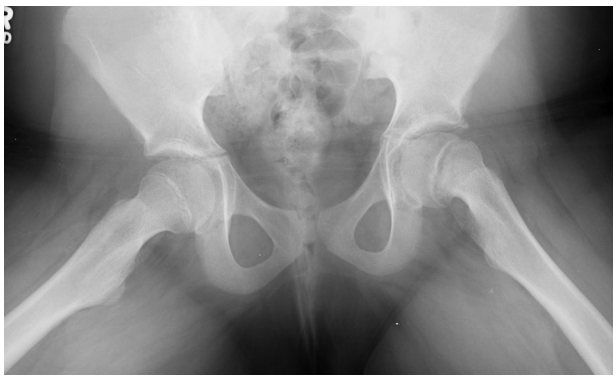

Figure 118.3. Anteroposterior pelvic radiograph of a patient with slipped capital femoral epiphysis.
Courtesy of Michael Diament, MD.

in adolescent athletes, particularly those who participate in running or jumping sports. Repetitive microtrauma causes partial avulsion of the patellar tendon at its insertion on the tibia. Individuals typically present with a localized bony prominence, swelling, and tenderness over the tibial tubercle at the insertion of the patellar tendon. Osgood-Schlatter disease can be diagnosed clinically, although radiographs are commonly obtained to rule out other pathology and typically demonstrate soft tissue swelling or edema of the skin and tissues, as well as ossific fragments within the tendon (Figure 118.4). Symptoms tend to resolve at approximately 14 to 15 years of age after the tibial tubercle closes.

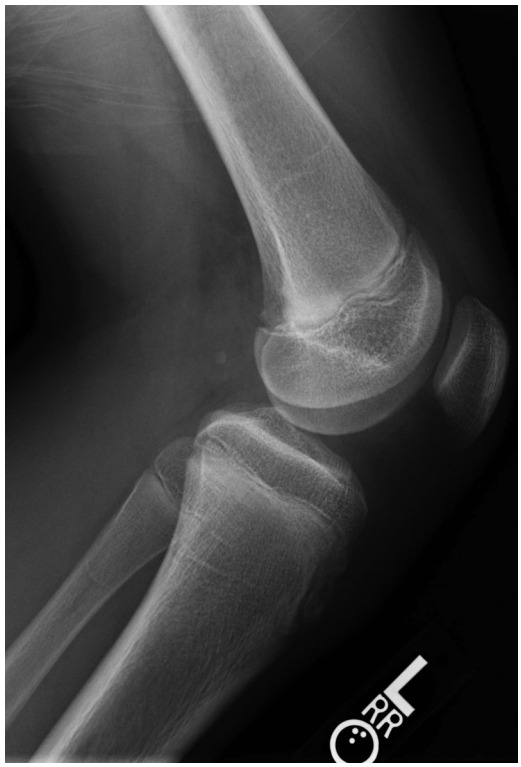

Figure 118.4. Lateral radiograph of the knee in a patient with Osgood-Schlatter disease.
Courtesy of Michael Diament, MD.

A limp can also result from certain systemic disease processes, such as juvenile idiopathic arthritis, SCD, Lyme arthritis, and neoplastic disease. Juvenile idiopathic arthritis may involve multiple joints or have an associated rash. Evidence of inflammation (eg, warmth, swelling or effusion, redness) is typical (see Chapter 156). Usually, the pain is worst in the morning and improves throughout the day. Currently, SCD is detected on newborn screening, and most patients know of their diagnosis. Acute pain crises with SCD can affect multiple areas, resulting in significant discomfort, limp, and refusal to walk. Careful consideration for infectious etiologies (ie, osteomyelitis) is necessary in the highly febrile or ill child with SCD who presents with a limp or bone pain. Additionally, patients with SCD are at risk of avascular necrosis of the hip secondary to vasoocclusive episodes. Patients with Lyme arthritis typically are able to bear weight despite having a joint effusion, most commonly in the knee. A patient may have had earlier clinical symptoms of Lyme disease, such as the target-sign lesion, erythema chronicum migrans, or a viral prodrome. Other disseminated symptoms include meningitis, carditis, and cranial nerve palsy. Diagnosis can be made via enzyme-linked immunosorbent assay and Western blot. The arthritis usually is self-resolving but can be managed with antibiotics. Neoplastic disease processes, such as leukemia and primary bone tumors (eg, Ewing sarcoma, osteosarcoma) can present with bone pain and limp. The presence of pallor, petechiae, disseminated lymphadenopathy, or hepatosplenomegaly may be suggestive of leukemia. Peripheral CBC usually shows the presence of blasts and varying degrees of involvement of the various cell lines (ie, anemia, thrombocytopenia). Primary bone tumors may present with bony deformities or overlying soft tissue swelling. Characteristic bony lesions often are evident radiographically, although MR imaging may be necessary to ascertain the extent of involvement. Computed tomography may be necessary to assess for metastases. It may be necessary to refer a patient to an orthopedic surgeon for biopsy to ascertain a definitive diagnosis and for possible amputation. Referral to an oncologist is necessary to initiate appropriate therapy, including chemotherapy or radiation.

Evaluation

History

The history should focus on the time of onset of the limp, chronicity, and the resulting degree of disability. Often, a history of trauma is provided, even in the setting of a nontraumatic cause. Young toddlers often fall as they learn to walk, and parents and caregivers frequently relay some trivial or unrelated injury. Delayed motor development may be a sign of neuromuscular disease (eg, cerebral palsy), whereas a history of loss of motor milestones may be indicative of muscular dystrophy or spinal cord tumor. It is important to remember that pelvic pathology may be referred to the hip, and hip pathology is often referred to the knee or thigh.

Physical Examination

Physical examination begins with observation for any overt deformity (eg, leg length discrepancy, joint swelling). All joints and the spine should be palpated, and the presence of swelling, tenderness,

erythema, or warmth should be noted. A thorough evaluation of the hips is essential in the child with knee pain. The type of gait abnormality may be determined by observing the child walk or run.

The child should be examined supine and standing, if possible. The standing child can be assessed for pelvic obliquity and spinal deformities. Range of motion of the hips, knees, ankles, and feet can be assessed in the supine child, comparing the affected side with the nonaffected side. Muscle strength should be assessed, and leg length measurements should also be obtained as indicated. The child should be supine for a true measurement of leg length, which is the distance from the anterosuperior iliac spine to the medial malleolus. A discrepancy of more than 2 cm is considered significant in adults. The significance of discrepancies can be confirmed on imaging studies.

Laboratory Tests

Laboratory studies are usually necessary in the child with an acute onset of limp with no clear trauma, especially in the child who refuses to bear weight or is febrile. Complete blood cell count, CRP, and ESR are useful markers of systemic disease and significant inflammation. Significant overlap may exist between the differing etiologies, and no single screening test can reliably distinguish between the various inflammatory and infectious causes of limp. Blood and local cultures (eg, joint fluid, bone) may be useful in the evaluation of suspected infectious entities. In addition to the culture, effusion studies should also include a cell count, Gram stain, glucose, and protein. Additional testing for rheumatologic causes may be clinically indicated, such as antinuclear antibody or rheumatoid factor (see Chapter 156).

Imaging Studies

Radiographs are the most commonly obtained images. At least 2 views should be obtained. For examination of the hip, both AP and batrachian views are necessary. It is important to include both hips in these images for comparison and to assess for the presence of bilateral disease. Ultrasonography is helpful if concern exists for an effusion within the joint space and can also be used to guide diagnostic and therapeutic interventions (eg, arthrocentesis) (Figure 118.5). Useful information is sometimes gleaned from CT, but MR imaging with gadolinium contrast is increasingly being used because of the superior resolution it affords and lack of radiation.

Management

Management depends on the etiology. Management of septic arthritis consists of surgical drainage and intravenous (IV) antibiotics. Empiric therapy typically consists of an antistaphylococcal penicillin (eg, nafcillin sodium, oxacillin sodium). In a region with high rates of community-acquired MRSA, administration of clindamycin or vancomycin may be necessary until sensitivities can be performed. The addition of a third-generation cephalosporin is often indicated pending Gram stain and culture results to cover gram-negative pathogens, such as *K kingae*, or in cases in which *N gonorrhoeae* is suspected in an adolescent patient. Length of therapy typically consists of 2 to 4 weeks of IV antibiotics. Prognosis is generally good with prompt diagnosis and management within 4 days of symptom onset. Nonsteroidal anti-inflammatory drugs and low-dose steroids can also be considered to manage inflammatory pain.

Initial management of osteomyelitis also consists of IV antibiotics. Occasionally, surgery may be indicated, particularly in the setting of a subperiosteal or soft tissue abscess or sequestra. In communities in which methicillin-susceptible *S aureus* is more prevalent, empiric antibiotic therapy consists of an antistaphylococcal penicillin (eg, nafcillin sodium, oxacillin sodium) or a first-generation cephalosporin (eg, cefazolin). In areas in which community-acquired MRSA is of concern, clindamycin or vancomycin may be necessary. Neonates and individuals with SCD require the addition of a third-generation cephalosporin pending culture results. In individuals with a presumed pseudomonal infection, an extended spectrum β-lactam (eg, ceftazidime, cefepime, piperacillin/tazobactam) plus an aminoglycoside are indicated. Currently, 4 to 6 weeks of antibiotic therapy is recommended. Increasing data support switching to oral

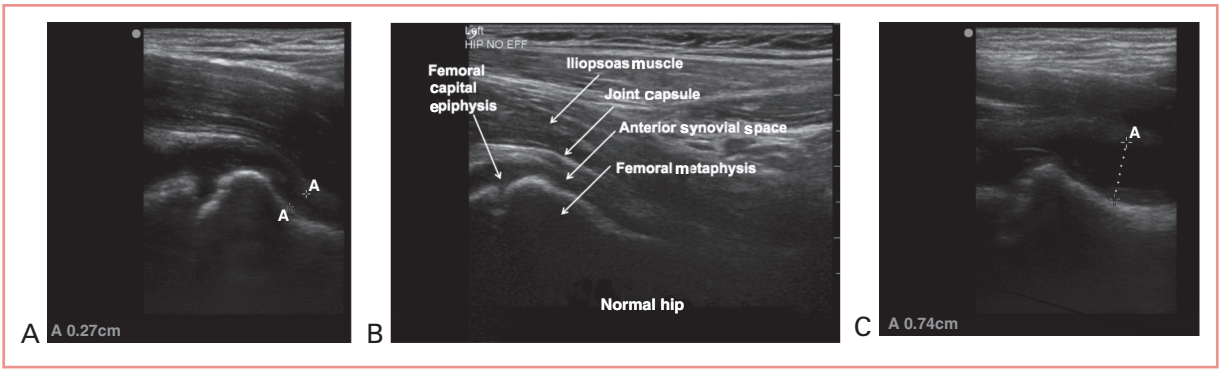

Figure 118.5. Ultrasound images of the hip. A, Anatomic landmarks in a hip ultrasound image illustrate normal joint space between the letters "A." B, A normal hip joint space measuring 2.7 mm. Normal is less than 5 mm or a difference of less than 2 mm compared with the contralateral hip. C, A notable hip effusion with a joint space measuring 7.4 mm indicated by the dotted line and letter "A."

Courtesy of Kathryn Pade, MD.

antibiotics after receiving as little as 2 to 4 days of parenteral therapy if compliance is likely, an organism has been identified, clinical improvement is noted, the patient is afebrile, and the inflammatory markers have begun to normalize. Oral dosages 2 to 3 times those normally recommended for nonosseous infections are often used for β-lactam antibiotics. Other oral antibiotics (eg, clindamycin, trimethoprim plus sulfamethoxazole, fluoroquinolone) have excellent bioavailability, and the usual oral dosages may be administered. Amoxicillin should be considered in children younger than 4 years who have not been vaccinated to cover *H influenzae*. Consultation with an infectious disease specialist is often indicated.

Supportive measures with NSAIDs are generally indicated for the management of diskitis. Broad-spectrum antibiotics are generally given, and the addition of anti-staphylococcal antibiotics should also be considered and have been shown to speed improvement of symptoms. A brace may be helpful for support and pain relief. Most patients recover without complications.

Prompt referral to an orthopedic surgeon is indicated in the patient with LCPD or SCFE. The goal of management of LCPD is to maintain full joint mobility and prevent femoral head deformity. Bed rest and immobilization decrease the pain and help restore range of motion. Traction and abduction casts or braces are used to contain the femoral head within the acetabulum in an effort to maintain its spherical shape. Surgical correction of gross deformities of the femoral head may be necessary in severe LCPD. Patients younger than 6 years are most likely to benefit from surgical treatment.

Management of SCFE consists of surgical reduction and stabilization with placement of screws through the epiphysis. The screws typically are left in place and do not need to be removed. Non-weight bearing is maintained until early callus is noted on the posteroinferior metaphysis and the pain has resolved. Gradual and progressive weight bearing is allowed, and progression to full weight bearing usually occurs 3 to 4 months after fixation. No running or jumping is allowed until the physis closes.

Treatment of OSD consists of rest, ice, NSAIDs, and strengthening exercises for the quadriceps and hamstring muscles. Surgical treatment is rarely indicated and is reserved for those patients who do not respond to nonsurgical therapy.

Prognosis

The prognosis depends on the etiology of the limp, time to diagnosis, and appropriate therapy.

In most cases of septic arthritis and osteomyelitis, the prognosis is good if the infection is diagnosed early and managed appropriately. The prognosis of osteomyelitis usually is good, with a less than 0.1% mortality rate and with less than 2% of patients who receive at least 3 weeks of antibiotic therapy developing chronic osteomyelitis. Management of chronic disease can be difficult, often necessitating prolonged courses of antibiotics (≤6–12 months) and multiple surgeries for débridement. Rare complications include disturbances in bone growth, leg length discrepancy, joint destruction, arthritis, abnormal gait, and pathologic fracture. Prognosis is also worse if treatment is delayed, the patient is younger, or the infection involves the hip, ankle, or knee. The main complication is degenerative arthritis of the hip. Regular follow-up with an orthopedic surgeon is necessary during the first year after diagnosis.

The prognosis of LCPD is related to the degree of femoral head involvement and age at onset of the disease. Children younger than 6 years have the best prognosis. The risk for developing degenerative arthritis in adulthood increases in children whose disease is more extensive and whose condition is diagnosed later (ie, after 8 years of age).

Untreated SCFE has the potential for further slippage of the femoral head until the growth plate closes. Potential treatment-related complications of SCFE include chondrolysis of the femoral head and acetabulum, avascular necrosis, and fracture at the site of pin placement. Generally, the prognosis is good and is based on the degree of slippage. The main complication is the development of avascular necrosis of the femoral head, which typically results in degenerative hip disease later in life. Degenerative hip disease later in life occurs in up to 15% of patients with SCFE and is more common in unstable SCFE. Only 7% of patients with a moderate slip have a poor outcome, compared with 24% of patients with a severe slip.

In approximately 5% to 10% of patients, OSD may become chronic, with persistent swelling and tenderness. In such cases, the formation of an ossicle over the tibial tubercle may be evident radiographically; because of the possibility that surgical resection of the ossicle may be required, the patient should be referred to an orthopedic surgeon.

CASE RESOLUTION

The child's history and physical examination seem to be consistent with LCPD. The child's knee pain is found to be secondary to hip pathology. The diagnosis may have been missed had the physician not examined the hips and noted the abnormality in range of motion. Anteroposterior and batrachian radiographs of the hips were obtained, which showed joint space widening. Orthopedic consultation was obtained, and hospitalization for bed rest and ensured immobilization were recommended.

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CHAPTER 119

Musculoskeletal Disorders of the Neck and Back

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CASE STUDY

A 4-week-old male infant is brought to the office by his mother, who reports that her son always holds his head tilted to the right. She states that he has held it in this position for approximately 1 week and prefers to look mainly to the left. The infant is the 3.86 kg (8 lb, 8 oz) product of a term gestation born via forceps extraction, and he had no complications in the neonatal period. He is breastfeeding well and has no history of fever, upper respiratory symptoms, vomiting, or diarrhea.

On examination, the head is tilted toward the right side with limited lateral rotation to the right and decreased lateral side bending to the left. Except for the presence of a small palpable mass on the right side of the neck, the examination is within normal limits.

Questions

1. What laboratory or radiologic studies are indicated in infants with torticollis?
2. What is the differential diagnosis of torticollis in infants?
3. What are some of the common musculoskeletal abnormalities that may occur in association with torticollis?
4. What are other common musculoskeletal problems in children and adolescents?
5. What is the current recommended management of children and adolescents with idiopathic scoliosis?

Children with disorders of the spine can present with deformity or back pain or occasionally, both. Atraumatic congenital and developmental deformities of the spine are frequently encountered in pediatric practice. Torticollis and scoliosis are 2 of the most common disorders in children that present as spinal deformity. *Torticollis*, or wry neck, is a positional abnormality of the neck resulting in abnormal tilting and rotation of the head. *Scoliosis* refers to any lateral curvature of the spine that measures more than 10° as determined on an anteroposterior radiograph of the spine. Scoliosis is classified as congenital, neuromuscular, or idiopathic. Idiopathic scoliosis itself is further categorized based on patient age: infantile, younger than 3 years; juvenile, 3 through 10 years; and adolescent, older than 10 years. Back pain is far less common in children than in adults. In children, such pain usually signals the presence of organic disease. In adolescents, however, back pain can result from musculoskeletal strain or from spondylolysis (ie, fracture of pars interarticularis).

Epidemiology

The most common type of torticollis in children is congenital muscular torticollis. The prevalence in the United States is estimated to be between 0.3% and 2% and is increased in breech presentations (eg, 1.8% breech presentation vs 0.3% vertex presentation). It occurs in up to 1 in 250 live births and is associated with developmental dysplasia of the hip (DDH) in up to 10% to 20% of affected infants. Family history may be positive in up to 10% of cases.

Acquired torticollis is much more common in older children and usually is secondary to trauma or infection, including cervical lymphadenitis, retropharyngeal abscess, myositis, and even upper respiratory tract infections. Episodes of benign paroxysmal torticollis, which often begin in the first year after birth and generally resolve by 5 years of age, may have a familial basis. An association with benign paroxysmal vertigo and migraines has been noted.

Some degree of spinal asymmetry or scoliosis occurs in approximately 2% to 5% of the population. Infantile scoliosis is rare in the United States and usually spontaneously resolves. The prevalence of juvenile scoliosis among school-age children in the United States is 3% to 5%. A right thoracic single curve is the most common curve seen by physicians. Seventy-five percent to 80% of cases of structural scoliosis are idiopathic, 10% are the result of neuromuscular causes, 5% are congenital, and the remaining 5% to 10% are the result of trauma or miscellaneous causes. Scoliosis that begins in childhood affects boys and girls equally, and affected boys outnumber girls from birth to age 3 years. Idiopathic scoliosis that manifests after age 10 years is more common in girls than boys, however, with a ratio estimated between 5:1 and 7:1. In children with cerebral palsy, the incidence of scoliosis is increased, occurring in approximately 20% of children with cerebral palsy.

Back pain is quite uncommon in preadolescent children. Unlike in adults, in whom it is often difficult to identify the cause, most instances of back pain in children have an identifiable etiology.

Clinical Presentation

Although torticollis may be noted at birth, it usually presents at 2 to 4 weeks of age. Infants with congenital muscular torticollis present with a characteristic head tilt toward the affected side with the chin pointing toward the opposite side; this positioning is secondary to unilateral fibrosis and contracture of the sternocleidomastoid muscle (Figure 119.1). Unrecognized or untreated torticollis may present as plagiocephaly (see Chapter 85) or facial asymmetry during infancy. Benign paroxysmal torticollis of infancy may present as recurrent episodes of head tilt that may be associated with vomiting, ataxia, agitation, or malaise (Box 119.1).

Mild scoliosis may not present with obvious deformity. Shoulder height asymmetry, scapular prominence or position, rib prominence or hump, waistline asymmetry or pelvic tilt, and leg length discrepancy may all be presenting signs of scoliosis (Box 119.1) (Figure 119.2A). Scoliosis may be detected during school-based screening programs or preparticipation sports physical examinations. Back pain is reported in 25% of adolescents with idiopathic scoliosis. When pain is present, further examination for some other cause (eg, bone tumors, spondylolysis, spondylolisthesis) is warranted. Preverbal children with back pain may present with limp or refusal to bear weight.

Pathophysiology

Torticollis may be either congenital or acquired. The etiology of congenital muscular torticollis is unknown. It is believed to be the result of intrauterine positioning or trauma to soft tissue of the neck during delivery, resulting in venous occlusion and ischemia of the sternocleidomastoid muscle. This causes edema and degeneration of the muscle fibers with eventual fibrosis of the muscle body. However, a prospective study of 821 patients with congenital muscular torticollis found that 55% of patients had a sternocleidomastoid tumor, 34% patients had thickening and tightness of the sternocleidomastoid, and 11% had head tilt without tumor or thickening of the sternocleidomastoid. Deformities of the face and skull may result if the condition is left untreated. Plagiocephaly (ie, cranial asymmetry), with flattening of the face on the affected side and flattening of the occiput on the contralateral side, is an associated finding.

Unlike kyphosis and lordosis, which are curves in the anterior-posterior plane, scoliosis is a lateral curvature of the spine occurring in the coronal plane. Scoliosis can be either functional (ie, nonstructural) or structural. In functional scoliosis, there is no fixed deformity of the spine and the apparent curvature disappears on lying down or on forward flexion. Individuals with leg length discrepancies may appear to have scoliosis but have no spinal abnormality.

Box 119.1. Diagnosis of Torticollis and Scoliosis in the Pediatric Patient

Torticollis

- Head tilt
- Limited neck range of motion
- Contracture of the sternocleidomastoid muscle
- Plagiocephaly associated with congenital torticollis
- Firm, nontender, mobile mass within the body of the sternocleidomastoid muscle (congenital torticollis with intramuscular hematoma)

Scoliosis

- Lateral curvature of the spine
- Some pain
- Back or truncal asymmetry

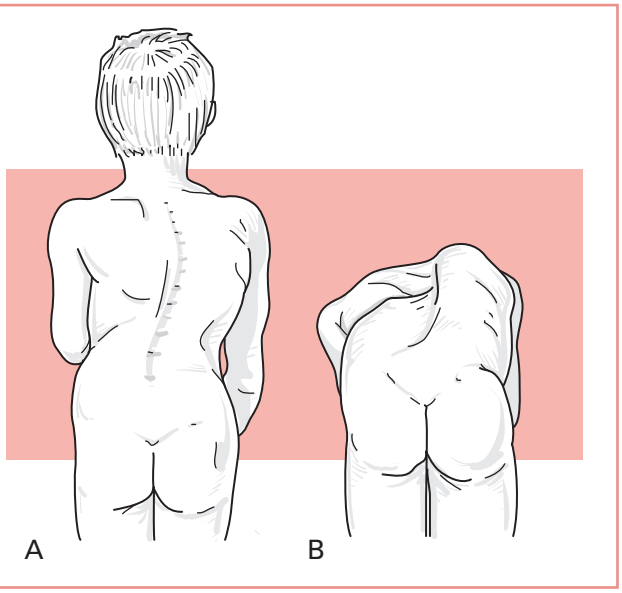

Figure 119.2. Illustration of a child with scoliosis. A, Rear view with the child standing. B, Rear view of the forward bend test.

Figure 119.1. Illustration of an infant with congenital muscular torticollis with the characteristic head tilt.

Structural scoliosis may be idiopathic or caused by various underlying disorders, such as muscular dystrophy or cerebral palsy in the nonidiopathic neuromuscular forms. The cause of idiopathic scoliosis is unknown, but there appears to be a higher incidence of scoliosis amongst other family members. Abnormalities of fibrillin have also been noted in some patients with scoliosis, a finding that is reported in patients with Marfan syndrome as well. In structural scoliosis, the spine has both a coronal curvature and a rotational component, which results in deformity of attached structures. For example, a "rib hump" may be produced as a result of scoliosis in the thoracic spine (Figure 119.2B). Pelvic obliquity or flank prominence may be produced when the curvature is in the lumbar spine.

Differential Diagnosis

The differential diagnosis of congenital and acquired torticollis is presented in Box 119.2. Torticollis not at birth is termed congenital muscular torticollis and is differentiated from acquired torticollis, which occurs in older infants and children and is secondary to another condition. When torticollis occurs in association with nystagmus and head nodding, this clinical triad is referred to as "spasmus nutans." Cervical lymphadenitis is a common cause of acquired torticollis that is seen in children 1 to 5 years of age, whereas trauma to the soft tissues or muscles of the neck is seen more frequently in school-age children. Acute episodes (eg, benign paroxysmal torticollis of infancy) must be differentiated from chronic conditions (eg, Sandifer syndrome, rheumatoid arthritis) based on the history.

Functional or nonstructural scoliosis may occur secondary to poor posture, leg length discrepancy, or muscle spasm. Structural scoliosis can be classified as idiopathic, congenital, neuromuscular, or miscellaneous (Box 119.3). Idiopathic scoliosis, which is by far the most common type of structural scoliosis, may be divided into 3 categories based on age: infantile (<3 years), juvenile (3–10 years), and adolescent (>10 years). The adolescent form occurs most frequently, accounting for up to 85% of cases.

Congenital scoliosis arises from anomalies in the development of the spine resulting in hemivertebrae or unsegmented vertebral bars. Because of the high incidence of anomalies in other body systems, such as cardiac and genitourinary anomalies, patients with congenital scoliosis require screening for associated abnormalities. Although neuromuscular scoliosis is most often seen in children with spastic cerebral palsy, it may be apparent in other conditions as well, such as poliomyelitis, meningomyelocele, muscular dystrophy, Friedreich ataxia, and spinal muscular atrophy. The miscellaneous causes of scoliosis are uncommon and include trauma, metabolic disorders, and neurocutaneous diseases.

The most common causes of back pain in children may be classified into 5 distinct categories (Box 119.4). When pain is significant enough that a child presents to the emergency department, common causes include trauma (25%), muscle strain (24%), sickle cell crisis (13%), idiopathic cause (13%), urinary tract infection (5%), viral syndrome (4%), and not categorized (16%). Other infectious causes, such as diskitis, occur much more frequently in children than adults. However, diskitis is rare in the pediatric population, with an estimated 1 to 2 cases per 32,500 pediatric emergency encounters. A child presenting with back pain should also be considered for an oncologic process, such as

Box 119.2. Common Causes of Torticollis

Congenital

- Congenital muscular torticollis
- Occipitocervical spine anomalies (eg, Klippel-Feil syndrome)
- Pterygium colli (ie, skin web)

Acquired

Infectious

- Cervical lymphadenitis
- Osteomyelitis of cervical vertebrae
- Retropharyngeal abscess

Traumatic

- Atlanto-occipital, atlas-axis (C1-C2), or C2-C3 subluxation
- Cervical musculature injury (eg, spastic torticollis)
- Cervical spine fractures

Neurologic

- Dystonic drug reactions
- Ocular disturbances (eg, strabismus, nystagmus)
- Syringomyelia
- Tumors located in the posterior fossa or cervical cord

Other

- Benign paroxysmal torticollis of infancy
- Hysteria
- Rheumatoid arthritis
- Sandifer syndrome (hiatal hernia with gastroesophageal reflux)
- Soft tissue tumors of the neck
- Spasmus nutans

Box 119.3. Common Causes of Scoliosis

Functional Scoliosis

- Back injury
- Herniated disk
- Leg length discrepancies
- Muscle spasm
- Poor posture

Structural Scoliosis

- Congenital
- Idiopathic
- Intraspinal tumors
- Marfan syndrome
- Metabolic disorders (eg, juvenile osteoporosis, osteogenesis imperfecta, mucopolysaccharidosis)
- Miscellaneous
- Neurocutaneous syndromes (eg, neurofibromatosis)
- Neuromuscular
- Trauma (eg, fractures or dislocations of the vertebrae)

Box 119.4. Common Causes of Back Pain in Children

Infectious
- Diskitis (more common in children younger than 5 years)
- Myalgias (eg, influenza)
- Referred pain (eg, pyelonephritis, pneumonia)
- Vertebral osteomyelitis (ie, pyogenic, tuberculous [ie, Pott disease])

Inflammatory
- Crohn disease/ulcerative colitis/psoriatic arthritis
- Disk space calcification
- Rheumatologic diseases (eg, juvenile rheumatoid arthritis, ankylosing spondylitis)

Neoplastic
- Benign tumors (eg, eosinophilic granuloma, osteoid osteoma)
- Metastatic disease (eg, neuroblastoma)
- Primary vertebral and spinal tumors (eg, Ewing sarcoma, osteosarcoma, neuroblastoma)

Developmental
- Scheuermann kyphosis (adolescents)
- Spondylolysis, spondylolisthesis (adolescents)

Traumatic
- Compression fracture of vertebrae
- Herniated nucleus pulposus (disk herniation)
- Ligamentous or muscle strain (eg, overuse syndromes)

Other
- Child abuse
- Osteoporosis (eg, rickets, osteogenesis imperfecta)
- Psychogenic
- Sickle cell crisis

Box 119.5. What to Ask

Torticollis
- Is there any family history of torticollis?
- What type delivery did the mother have (eg, cesarean section, vaginal delivery)? Were forceps required?
- When was the head tilt first noticed?
- Does the infant move the neck in all directions, or does the infant always prefer to look in 1 direction?
- Does the infant have any recent history of trauma to the head or neck area?
- Is the head tilt persistent, or does it come and go?
- Has the infant been sick or febrile?
- Does the child exhibit nystagmus or head bobbing?

Scoliosis
- Is there a family history of scoliosis?
- Have the parents or guardians noticed the curvature of the spine? If so, how old was the child when the condition was first noted?
- Has the curvature increased since it was first noticed?
- Does the child have any back pain?
- Has the child had any previous treatment for the condition?
- (If appropriate): Has the child begun menstruating?
- Is the child experiencing neurologic symptoms?
- Does the child have concerns about cosmesis?

Back Pain
- How long has the child had the pain?
- Where is the pain localized?
- Is the pain persistent, or does it come and go?
- Does the pain radiate anywhere (eg, down the legs)?
- Is the child limping or having difficulty walking?
- Has the child lost any motor milestones (eg, skills such as walking or standing that the child could previously perform)?
- What makes the pain better? What makes it worse?
- Is there a recent history of trauma, or has the child begun participating in a new sport or physical activity?
- Has the child had a fever?
- Has the child had any problems with bowel or bladder function?
- Is the child taking any medication?

osteoid osteoma, osteoblastoma, or hemangioma. Because the spine of children is smaller and has greater flexibility and ligamentous strength than the adult spine, children are at lower risk of traumatic injury than adults. Common causes of back pain in adults, such as musculoskeletal back pain (ie, muscle strain) and discogenic pain, are uncommon in children. Individuals who are predisposed to musculoskeletal back pain often experience their first episode during adolescence or young adulthood; only 1% to 4% of disk herniations occur in children.

Evaluation

History

A careful history may provide clues to diagnosis and etiology (Box 119.5). Approximately 25% of adolescents with scoliosis experience back pain.

Physical Examination

In the child with suspected torticollis, a thorough examination with specific attention to the head and neck region should be performed. Limited head rotation toward the affected side with decreased lateral side bending to the opposite side may occur. During the first 4 to 6 weeks after birth, a firm, nontender, mobile mass (ie, pseudotumor) may be palpated within the body of the sternocleidomastoid muscle; the mass gradually regresses by 6 months of age. Because torticollis is associated with DDH, the hips should be examined for stability. A neurologic examination should also be performed for any neurologic deficits that may be indicative of an underlying tumor. Fever or signs of inflammation are indicative of infectious causes. Because torticollis may be secondary to visual disturbances (eg, strabismus), a careful eye examination is warranted. The presence of nystagmus or head nodding is suggestive of spasmus nutans.

Screening for scoliosis should be part of the routine health maintenance examination of school-age children and adolescents.

Children should be examined with the back fully exposed. School screening methods have proven to be effective for evaluation and early referral to an appropriate health professional. The posture should be observed from the front, back, and both sides. The presence of any skin lesions, such as café au lait spots, should be noted. Any midline skin defects, such as dimples or hair patches, also should be noted because often they are associated with underlying spinal lesions. The spine should be palpated for any signs of tenderness, and a complete neurologic examination should be performed.

The back should be observed for asymmetry of the shoulders, scapulae, or pelvis. The Adam's Forward Bend Test may demonstrate a characteristic rib hump. The physician should have the child bend forward at the waist to an angle of 90° with the knees straight and the palms held together. This maneuver accentuates the curvature of structural scoliosis and emphasizes the rotational deformity of the spine. For example, in thoracic scoliosis, a characteristic rib hump is apparent on the convex side of the curve (Figure 119.2B). A scoliometer can be used to estimate the degree of scoliosis. More than 7° of rotation correlates with a Cobb angle of 20° and warrants referral to an orthopedic surgeon. Screening using a scoliometer in combination with the forward bend test is effective in early identification and screening.

Scoliosis is described in terms of the primary (ie, major) curve. The major curve may be accompanied by a secondary (ie, minor) curve. The location of the curve is defined by the apical vertebra (eg, T2-T11, thoracic; T12-L1, thoracolumbar), the direction of the curvature by the side of convexity, and the severity by the degree of curvature as measured on the spinal radiograph. Curves greater than 15° are abnormal. Mild scoliosis is defined as curvature of less than 20°, moderate as curvature of 20° to 40°, and severe as curvature greater than 40° to 45°.

The evaluation of back pain begins with observation of the child's posture and gait. Any midline skin lesions should be noted. A thorough general physical examination is important, because referred pain (eg, pancreatitis, pyelonephritis, nephrolithiasis) may be causing the symptoms in the back. The spine should be palpated for any signs of tenderness. A complete neurologic examination should be performed, and any motor or sensory deficits should be noted. The motor examination should emphasize evaluation of the hips and the lower extremities, including range of motion and strength. Any "red flag" symptoms associated with back pain should raise concern for an oncologic process.

Laboratory Tests

In cases of congenital torticollis, laboratory studies are rarely necessary. In the patient with acquired torticollis in whom infection is suspected, however, a complete blood cell count and blood and local cultures may aid in the diagnosis.

No specific laboratory tests are required in the evaluation of idiopathic scoliosis. Specific laboratory studies may be performed in the evaluation of other forms of scoliosis as indicated by the history and physical examination (eg, urine metabolic screening for suspected metabolic disturbances).

Laboratory assessment for back pain depends on the history and physical examination. A complete blood cell count, blood culture, and erythrocyte sedimentation rate may be useful in the evaluation of suspected infectious etiologies. After the diagnosis of diskitis is established, image-guided aspiration or blood cultures should be drawn to identify the bacterial organism. Rheumatologic studies, such as a rheumatoid factor or human leukocyte antigen typing, may aid in the diagnosis of inflammatory conditions. If the back pain is of acute onset, a laboratory study may be warranted to determine whether the pain is referred rather than musculoskeletal. For example, urinalysis or a serum amylase test may be performed to diagnose pyelonephritis or pancreatitis, respectively.

Imaging Studies

In the child with suspected torticollis, radiographs generally are not useful unless bony anomaly is suspected. Anteroposterior and lateral views of the cervical spine can identify subluxation of C1-C2; however, less than 1% of children with torticollis have a subluxation. Ultrasonography may reveal the location of a sternocleidomastoid mass. Magnetic resonance (MR) imaging of the sternocleidomastoid muscle mass may be considered if an underlying condition (eg, branchial cleft cyst) is suspected. Computed tomography or MR imaging of the head or cervical spinal cord is indicated if a neurologic tumor is suspected.

Routine radiographs are not required in the evaluation of all children with mild scoliosis (ie, minor degrees of curvature noted on physical examination). It may be best to obtain radiographs after orthopedic evaluation is complete. Radiographic imaging should be used as sparingly as possible to limit the radiation dose incurred by the child during the course of treatment of the scoliotic curve. Standing posteroanterior and lateral spine radiographs are obtained to determine the location and direction of the curvature, measure the degree of asymmetry (ie, Cobb angle), and evaluate the vertebrae. Shoe lifts should be used prior to radiography to compensate for leg length discrepancy. Repeat radiographs of the spine are obtained to follow the progression of the curvature over time. Because the risk of curve progression before skeletal maturity is a primary concern, radiographs of the hand and wrist should be obtained to assess bone age in the prepubertal child with scoliosis. Magnetic resonance imaging is recommended in the individual with rapid progression of the curve (ie, 1° per month), an atypical curve (eg, left thoracic curve), or abnormal physical examination findings (eg, abnormal abdominal reflexes). Magnetic resonance imaging should include the cervical, thoracic, and lumbar spine to identify deformities such as Arnold-Chiari malformation, tethered cord, or syrinx.

As with scoliosis, routine radiographs are not indicated in all patients with back pain. Various radiologic studies may be ordered depending on the suspected diagnosis. Radiographs may be useful in the evaluation of suspected vertebral abnormalities, such as spondylolysis and spondylolisthesis. However, these conditions may represent incidental findings and may not be the source of the back pain. If diskitis is suspected, bone scanning may be more appropriate than radiography. Similarly, bone scanning or MR imaging is useful in the evaluation of suspected vertebral tumors.

Management

Management of congenital muscular torticollis consists of passive stretching exercises of the neck. With the neck in a neutral position (ie, not in hyperextension), the head is bent to 1 side so that the ear on the side opposite to the contracted muscle is brought to the shoulder, or alternatively the chin is lowered to touch the shoulder on the affected side. These exercises are done 3 times per week, with each session consisting of 3 repetitions of 14 manual stretches of the affected sternocleidomastoid muscle. Additionally, changing the placement of the crib in relation to the nursery door and repositioning toys and mobiles in the crib stimulate children to look toward the side opposite the preferred gaze. The child should also be fed with the chin turned toward the shoulder of the affected sternocleidomastoid muscle. Torticollis resolves spontaneously in most infants. When the deformity persists beyond the age of 1 to 2 years, surgical release of the contracted muscle may be indicated. Newer, less invasive methods of arthroscopic or radiofrequency release under local anesthesia have been proposed and used to provide better functional outcomes and reduce the risks associated with open surgical procedures.

Management of acquired torticollis is dependent on the etiology. The evaluation and management of many of these conditions can be complex and often requires consultation with specialists in otolaryngology, head and neck surgery, neurology, and orthopedic surgery.

The 3 types of management of scoliosis are observation, bracing, and surgery. An estimated 10% of individuals with adolescent idiopathic scoliosis require some form of treatment. Observation involves close follow-up with careful repeat physical examinations and radiographic studies. The child who has not undergone the rapid growth phase is at greatest risk of marked progression of the curve. The Risser sign is a common radiographic tool to estimate skeletal maturation. The sign is based on the degree of ossification of the iliac apophysis, with Risser 0 signifying no ossification and Risser V representing full ossification. An initial consultation with an orthopedic surgeon is generally advisable, even for minor degrees of curvature. The goal of follow-up is early detection of curvature with implementation of treatment to prevent or minimize curve progression. The child with a curve of less than 20° to 25° should undergo assessment every 4 to 6 months at a specialist clinic to monitor for curve progression. To minimize radiation exposure, only posteroanterior radiographs are obtained at each subsequent visit. A curve of between 25° and 45° in the skeletally mature individual (ie, Risser IV or V) does not require bracing; however, such curves should be braced (eg, with a Milwaukee brace) in the growing child (ie, Risser 0 or I). The goal of bracing is not to correct any existing curvature but to prevent further curve progression. The efficacy of bracing is determined by adherence to the regimen; however, poor compliance is common and is thought to be the result of social ostracism. Evidence has shown that greater than 18 hours of wear daily is required to achieve optimal results. Surgery (eg, Harrington rod placement, posterior spinal fusion) may be indicated for the child with a curve of greater than 45° to 50°. These curves have a high likelihood of progression into adulthood. The goals of surgery include arrest of curve progression, improved cosmesis, and improved functional capacity. The development of pedicle screws has advanced the process of spinal fusion.

Although the management of back pain is diagnosis dependent, rest and immobilization are principles of treatment that apply in many instances. Management of diskitis is reliant on culture-specific antibiotics, and surgery usually can be avoided. If spondylolisthesis and spondylolysis are not responsive to rest and immobilization, surgical stabilization may be required. In the adolescent with low back pain related to muscular injury, conservative treatment, including bed rest, heat, and nonsteroidal anti-inflammatory drugs, may be tried for 1 to 2 weeks followed by a gradual return to normal activity. It is not advisable to institute such treatment in younger children without pursuing a more extensive evaluation or consultation with an orthopedic surgeon, because the risk of serious disease is significant in this age group.

Prognosis

Congenital muscular torticollis responds to conservative management in approximately 90% of infants. The asymmetry of the face and skull also corrects over time after the contracture of the sternocleidomastoid muscle resolves. Spasmus nutans, which manifests between 4 and 12 months of age, usually resolves spontaneously by 3 years of age.

The direction and location of the curvature in scoliosis do not change with age; however, the degree of curvature may remain stable or progress. The earlier the age of onset, the worse the prognosis because of the amount of remaining growth and the potential for curve progression. Factors associated with a high risk of curve progression include female sex, a positive family history for scoliosis, younger age at diagnosis (especially before the adolescent growth spurt), and a larger curve at the time of diagnosis. Additionally, a double curve is more likely to progress than a single curve, and a thoracic curve is more likely to progress than a lumbar curve. Left untreated, severe scoliosis can cause cardiopulmonary impairment or cosmetic deformity, resulting in low self-esteem and poor body image. Decreased exercise tolerance has been reported in individuals with curves as small as 20°. Individuals with infantile and juvenile scoliosis can experience increased mortality from pulmonary and cardiac conditions during their 40s and 50s in comparison to the adolescent form.

Most cases (80%–90%) of low back pain in adolescents and young adults resolve spontaneously in 2 to 8 weeks. It is important for patients to learn how to prevent recurrence by improving posture, learning how to lift heavy objects appropriately, and instituting a program of exercises to help strengthen the muscles of the abdomen, back, and core stabilizers.

CASE RESOLUTION

The history of the infant is consistent with congenital muscular torticollis. Physical examination helps confirm the diagnosis. The hips should be evaluated thoroughly because of the association of congenital muscular torticollis with DDH. A program consisting of neck stretching exercises and repositioning of interesting toys and objects in the infant's crib to the side opposite the preferred gaze should be instituted. The infant can be reevaluated in 2 to 3 weeks to monitor progress.

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PART 11

Gastrointestinal Disorders

CHAPTER 120

Vomiting

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CASE STUDY

A 10-month-old previously healthy infant was brought to the emergency department by his mother, who reported the sudden onset of green emesis and abdominal pain over the last 4 hours. Vomiting was not associated with meals. The mother denied recent illness, travel, or sick contacts. The patient's past medical history is unremarkable. His birth weight was 3,200 g (7.05 lb), and his current weight is 9,080 g (20.0 lb). The physical examination is significant for distended abdomen tender to palpation.

Questions

1. What is the mechanism of vomiting?
2. What are the common causes of vomiting in newborns and infants?
3. What are the common causes of vomiting in older children?
4. What is the significance of bilious vomiting?
5. What are the unique features of vomiting related to increased intracranial pressure?
6. What are some strategies for the management of vomiting in older children?

Vomiting is a common symptom in infants and children and led Thomas Phaire to write, "Many tymes the stomake of ye child is so feble that it cannot retayne eyther meate or drynke..." (*The Boke of Chyldren*, 1544). *Vomiting* is defined as the forceful ejection of the stomach contents through the mouth. The mechanism involves a series of complex, neurologically coordinated events under the control of the central nervous system (CNS). Vomiting is often accompanied by autonomic signs such as pallor, diaphoresis, hypersalivation, listlessness, and tachycardia. Nausea and vomiting are common symptoms in infants and children and may be associated with gastrointestinal (GI) illnesses, other acute or chronic disorders, and medications.

In contrast, *regurgitation* (commonly called "spitting up" by parents) is the effortless bringing up of 1 or 2 mouthfuls of food without distress or discomfort. This is a frequent symptom of gastroesophageal reflux in infants (see Chapter 121). *Rumination,* a form of autostimulation, is the voluntary induction of regurgitation. It is most often noted in infants between the ages of 3 and 6 months. Rumination occurs in infants with developmental delays or with a disturbed mother-infant relationship. Rumination should be considered in infants from deprived environments (eg, neglectful homes).

Epidemiology

Fifty percent of infants have spitting up or vomiting as an isolated symptom, and less than 5% of these infants have significant underlying disease. Vomiting occurs less frequently in older children, who often experience acute, self-limited illnesses, such as gastroenteritis.

Clinical Presentation

Vomiting is categorized by its color (bilious or non-bilious) and temporal pattern (ie, acute, chronic, or cyclic [episodic]). The vomitus is considered bilious if it has a green or bright yellow color, indicative of large amounts of bile in the stomach and usually associated with intestinal obstruction. When vomiting occurs suddenly in a previously healthy child, it is acute. Most frequently, vomiting is related to acute gastroenteritis, urinary tract or other extraintestinal infections, or toxic ingestion. Acute vomiting may be indicative of a surgical condition, such as appendicitis, intestinal obstruction, or other acute condition. Chronic vomiting consists of a low-frequency (ie, once or twice daily) vomiting that never leads to dehydration. Chronic conditions such as peptic ulcer disease, Crohn disease, and cow's milk protein allergy can be associated with chronic vomiting. Children with cyclic vomiting experience intense, unremitting nausea and paroxysmal vomiting lasting hours to days, often leading to dehydration.

Infants and children may present with vomiting as an isolated symptom or in association with other symptoms, including faintness, diaphoresis, sweating, pallor, tachycardia, fever, anorexia, abdominal pain, and diarrhea (Box 120.1). When vomiting has persisted over a period, weight loss or failure to thrive (FTT) may occur. Neurologic symptoms, including headache and gait disturbances, may be noted in children with CNS problems. Other neurologic symptoms of altered muscle tone, lethargy, seizures, or coma in young infants suggest inborn errors of metabolism.

Pathophysiology

Vomiting is a reflex reaction that occurs in response to numerous stimuli, such as enteric infections, toxins, drugs, chemotherapy, and radiation. The final common pathway involves expulsion of food from the relaxed stomach into the mouth due to coordinated contraction of the abdominal wall, respiratory muscles, increased

Box 120.1. Diagnosis of Vomiting in the Pediatric Patient

- Nausea
- Abdominal pain
- Anorexia
- Diarrhea
- Headache
- Fever
- Lethargy

intra-abdominal and thoracic pressure, and relaxation of the lower and upper esophageal sphincters.

Anything that delays gastric emptying may be associated with vomiting. Gastric emptying may be delayed by a high-fat meal, swallowed mucus (eg, maternal mucus after birth, nasal mucus with an upper respiratory infection), fever, infection, and malnutrition. Delayed gastric emptying may develop with long-standing diabetes mellitus.

Vomiting can be divided into 3 phases: nausea, retching, and emesis. However, nausea may occur without retching and vomiting, and retching may occur without vomiting.

Nausea is a significant and difficult-to-define discomfort related to the sensation of a need to vomit. It can be produced by various stimuli (eg, bacterial toxins, drugs, intestinal distention, visceral pain, unpleasant memories, labyrinthine stimulation, noxious odors, visual stimulations, unpleasant taste, increased cerebral pressure). Peripheral receptors in the stomach and the small and large intestines detect emetic stimuli, distention and contractions are recognized by mechanoreceptors, and toxins are sensed by chemoreceptors. Emetic stimuli may also originate from the obstructed or inflamed bile ducts, peritoneal inflammation, mesenteric vascular occlusion, pharynx, and heart. Vagal pathways mediate emetic responses to a variety of peripheral stimuli. Most afferent vagal fibers project to the nucleus tractus solitarius and some to the area postrema or dorsal vagal motor nucleus. The serotonergic pathway plays the central role in nausea induced by peripheral stimuli.

The area postrema on the dorsal surface of the medulla close to the fourth ventricle is considered the chemoreceptor trigger zone to a variety of neurochemical stimuli. Bacterial toxins, drugs, toxic products of metabolic disorders, and radiation therapy may induce nausea by stimulation of numerous central receptors: dopamine D_2, muscarinic M_1, histaminergic H_1, serotonergic 5-HT3, and vasopressinergic subtypes located in the area postrema. However, afferent excitation of multiple brain sites, including the nucleus tractus solitarius, dorsal vagal and phrenic nuclei, medullary nuclei controlling respiration, hypothalamus, and amygdala, is responsible for coordinated activities of various organs and muscles and the induction of retching and emesis.

Retching is the second phase of vomiting. It is produced by concurrent contractions of inspiratory thoracic, diaphragmatic, and abdominal muscles against the closed glottis. The generated high positive intra-abdominal pressure forces gastric contents into the esophagus and herniates the gastric cardia into the thorax. At this phase, the high negative thoracic pressure prevents emesis of gastric fluids.

Emesis is the final stage of vomiting. Synchronous contractions of the inspiratory and expiratory muscles generate high positive intrathoracic pressure sufficient to produce expulsion of gastric contents into the mouth. Oral propulsion of the vomitus is facilitated by the elevation of the hyoid bone and larynx. Airways are protected from aspiration by glottis closure. Elevation of the soft palate prevents passage of the vomitus into the nasal cavities. Hyperventilation may occur before emesis. During vomiting, breathing is suppressed.

With emesis, retrograde giant contractions originate from the middle of the small intestine. Intestinal contents move into the stomach, causing duodenogastric reflux. Within the stomach, the fundus remains flaccid, but the antrum and pylorus contract. Relaxation of the lower esophageal sphincter also occurs.

In children with pyloric stenosis, duodenogastric reflux is prevented by hypertrophy of the pylorus. Projectile vomiting is facilitated by giant, often-visible contractions of the antrum and relaxation of the proximal stomach and low esophageal sphincter. Nausea is not associated with vomiting related to pyloric stenosis, and affected infants are frequently eager to eat immediately after vomiting.

Vomiting induced by increased intracranial pressure (ICP) is also not associated with nausea. In addition, such vomiting frequently occurs first thing in the morning on awaking and on an empty stomach. Regurgitation is a return of undigested food back up the esophagus to the mouth without the force and displeasure associated with vomiting. It could be manifested by visible spitting up after feeding or could be silent. Clinical evidence of regurgitation is not always associated with gastroesophageal reflux disease.

Differential Diagnosis

Vomiting can be a manifestation of GI, renal, metabolic, allergic, and CNS disorders, and the age of the patient influences the differential diagnosis and management. Some conditions respond to medical management, and others mandate surgical intervention (Box 120.2). The green color of the vomitus, referred to as *bilious vomiting,* is a serious sign, usually indicative of intestinal obstruction distal to the major duodenal papilla and of the need for surgical intervention. Bilious vomiting can also occur in children with pseudo-obstruction or acute pancreatitis and other conditions associated with paralytic ileus.

The presence of blood in the vomitus is another ominous sign and is discussed in Chapter 122.

The most common cause of vomiting is acute viral or bacterial gastroenteritis. Acute gastroenteritis is discussed in greater detail in Chapter 123. In cases that are not related to acute gastroenteritis, considering the age of the patient is the best approach to the differential diagnosis of vomiting.

Newborns and Infants

Vomiting in neonates may be associated with the ingestion of irritants such as maternal blood or mucus. Either of these substances

Box 120.2. Differential Diagnosis of Vomiting in Infancy

Medical Conditions

- Gastroenteritis
- Ingestion of maternal blood or mucus
- Overfeeding
- Food allergies
- Gastroesophageal reflux

Surgical Conditions

- Atresia/stenosis of gastrointestinal tract
- Pyloric stenosis
- Volvulus
- Inborn errors of metabolism
- Congenital adrenal hyperplasia
- Infections (eg, otitis media, urinary tract)
- Congenital megacolon (Hirschsprung disease)
- Intussusception
- Appendicitis

delays gastric emptying. Structural anomalies of the GI tract may also cause vomiting in neonates. The onset of symptoms is directly related to the level of obstruction—the higher the structural obstruction, the earlier the onset of vomiting. Lesions of the esophagus, such as esophageal atresia, may be evident in the delivery room, with an unsuccessful attempt to pass a nasogastric tube. Lower GI lesions, such as ileal atresia, may not present for several days. These lesions require surgical intervention. Infants with atretic lesions may also have a history of polyhydramnios or a single umbilical artery.

Overfeeding is the most common reason for regurgitation in young infants. Frequently, infants who present with vomiting are actually experiencing regurgitation. Overfeeding is less likely to occur in breastfed infants because they have better control of their satiety. The physician should approach breastfed infants who are vomiting with care and concern.

Mothers of formula-fed infants may feel that the volume of formula consumed by their infants is insufficient. Some non-nursing mothers feel the need to reinsert a nipple in the infant's mouth, and infants who are still interested in nonnutritive sucking continue to feed, often exceeding the capacity of the stomach.

Food allergies are another common cause of vomiting during infancy. Infants with cow's milk formula intolerance may experience vomiting. At least 30% of these infants are also allergic to soy protein. Associated symptoms such as diarrhea, rhinorrhea, eczema, and growth failure frequently occur.

Gastroesophageal reflux is a common cause of regurgitation. It is described in detail in Chapter 121.

Achalasia, which is a rare cause of vomiting during infancy, is defined as an absence of effective esophageal peristalsis and coordinated relaxation of the low esophageal sphincter. Ingested food that is unable to pass into the stomach may be regurgitated. Children with achalasia usually do not present until later in childhood, although they may have a prenatal history of polyhydramnios, a sign suggesting an abnormal swallowing pattern, even in utero.

Metabolic disorders, including inborn errors of metabolism and endocrine problems, may also be associated with vomiting. For example, children with galactosemia may present with vomiting as well as with jaundice, dehydration, cataracts, and hepatomegaly. Other inborn errors of metabolism include methylmalonicacidemia, disorders of the urea cycle, phenylketonuria, maple syrup urine disease, renal tubular acidosis, hypercalcemia, and diabetes insipidus. Some of these disorders induce symptoms suggestive of sepsis, such as lethargy and seizures.

Male newborns and infants with congenital adrenal hyperplasia may present with vomiting and electrolyte disturbance, symptoms indicative of adrenal insufficiency. Affected male newborns usually present at about 10 to 14 days of age with vomiting and hyperkalemia (which should not be attributed to hemolysis of the specimen); hyponatremia manifests later. In females, congenital adrenal hyperplasia is usually detected in the newborn nursery because of ambiguous genitalia. Diagnosis of this potentially lethal condition is critical to ensure the institution of replacement therapy and survival of affected newborns and infants.

Vomiting may be induced by infection in parts of the body other than the GI tract. Most notably, urinary tract infections (UTIs) in infants may cause projectile vomiting, a symptom highly suggestive of pyloric stenosis. These infants are usually febrile, and the diagnosis is considered when the urinalysis or culture result is positive. Otitis media may also be associated with vomiting.

Vomiting, especially if unrelated to meals, may occur with increased ICP. In young infants, this suggests the possibility of an intracranial hemorrhage, such as that which occurs with abusive head trauma.

Pyloric stenosis, a condition caused by hypertrophy of the muscle surrounding the pyloric channel, is the most common surgical condition associated with vomiting in infancy. The condition affects males significantly more frequently than females and usually appears in newborns and infants between the ages of 2 weeks and 2 months. Factors that are known to increase the risk of pyloric stenosis include being firstborn and male and having a greater birth weight and early exposure to erythromycin. The emesis is projectile and non-bilious and frequently contains curdled milk, which reflects delayed gastric emptying, a problem caused by failure of the hypertrophied pylorus to relax. Affected newborns and infants have an intact appetite and are eager to eat. In some newborns and infants, starvation leads to few bowel movements and constipation; in others, there may be small, frequent, mucus-laden stools (ie, starvation diarrhea) that represent intestinal juice. If pyloric stenosis is not diagnosed promptly, newborns and infants may fail to gain weight or may exhibit FTT. Symptoms suggestive of pyloric stenosis may result from an antral membrane or duplication of the GI tract.

Children

Vomiting in children is frequently associated with gastroenteritis. Infections elsewhere in the body, particularly UTIs, streptococcal

pharyngitis, and otitis media, are also associated with vomiting. Labyrinthitis presents with vomiting associated with dizziness. Older children with new-onset diabetes mellitus may present with vomiting. Vomiting may also appear in children who are already known to have diabetes; this is particularly true when ketosis is present. Slow gastric emptying (ie, gastroparesis) is a complication of long-standing diabetes mellitus. Vomiting is also a component of peptic ulcer disease, which is described in more detail in Chapter 125.

Vomiting may be a major symptom of CNS-related problems, such as tumors, infections, hydrocephalus, malformations, and other causes of increased ICP. As previously noted, vomiting associated with CNS-related conditions is often unrelated to meals and may not be associated with nausea. Autonomic epilepsy and migraine headaches are also associated with vomiting. Cyclic vomiting is an unusual condition characterized by recurrent episodes of vomiting with intervals of complete wellness between attacks. There is a frequent association of cyclic vomiting with a family history of migraine headaches. Emotional upset and other factors, such as infection and physical exhaustion, can precipitate events. As a rule, cyclic vomiting lasts an average of 2½ to 5½ years, resolving in late childhood or early adolescence. A few patients continue to be symptomatic through adulthood.

Vomiting is among the hallmarks of Reye syndrome, a disorder that involves an encephalopathy in association with fatty infiltration of the liver. The etiology of the condition is unclear, but the root of the disorder seems to be related to mitochondrial dysfunction. Affected children usually have a history of viral illness, most commonly influenza or chickenpox. Following a period of recovery, they experience altered consciousness with vomiting. Hepatic enzymes and serum ammonia are elevated. Aspirin, which uncouples oxidative phosphorylation, is apparently linked to Reye syndrome, epidemiologically as well as theoretically. There has been a marked reduction in the incidence of Reye syndrome related to the decrease in the use of aspirin as well as for children vaccinated against varicella and influenza.

Certain medications, including theophylline, erythromycin, and digitalis, may also be associated with vomiting. Some of these medications cause transient relaxation of the lower esophageal sphincter; others affect the chemoreceptor trigger zone.

Familial dysautonomia (also called Riley-Day syndrome), a rare condition that affects Ashkenazi Jews almost exclusively, results in vomiting. The disorder is inherited in an autosomal-recessive manner and consists of an imbalance in the autonomic nervous system. Children experience intractable vomiting in addition to excess perspiration, inability to produce tears, difficulty swallowing and chewing, and cold hands and feet. They also have hyperpyrexia and hypertension. These children require fluid replacement and management with antiemetics.

Surgical conditions such as appendicitis, gall bladder disease, and twisted ovarian cysts are discussed in Chapter 125.

Adolescents

Vomiting during the adolescent years may be caused by any of the previously mentioned conditions. In addition, adolescents may develop vomiting in association with intentional ingestion of illicit drugs or alcohol. Many adolescents have incorrect notions of the sexual activity needed to initiate pregnancy; teenaged girls who have been vomiting, especially for a time, should be evaluated for pregnancy, regardless of their disclosed sexual activity status.

Adolescents with eating disorders, particularly bulimia, vomit but may not disclose their vomiting. They may ingest emetics, such as ipecac, to help control their weight (see Chapter 64).

Evaluation

History

A complete history is essential for correct diagnosis (Box 120.3). A positive family history of vomiting may suggest a diagnosis of food intolerance or allergy, gastroesophageal reflux or peptic ulcer disease, migraine, or familial dysautonomia.

Physical Examination

The examination can show the effect of vomiting on children's growth. The weight may provide evidence of the chronicity of the process; weight loss suggests a protracted course. Evidence of other infections, such as otitis media or pneumonia, may also be apparent. An abnormal neurologic examination would suggest a CNS process or an inborn error of metabolism. The fundi of the eyes should be assessed for the presence of papilledema or retinal hemorrhages. Nystagmus may be noted in children with labyrinthitis or CNS disturbances. The examination of the abdomen may show abdominal distention due to surgical or nonsurgical conditions such as Hirschsprung disease, malrotation, adhesions after previous surgery, pancreatitis, celiac disease, chronic idiopathic constipation, and abdominal, pelvic, or retroperitoneal masses.

Laboratory Tests

Laboratory assessment is determined by the differential diagnosis. If gastroenteritis or enterocolitis is suspected, an examination of the stools for leukocytes and occult blood is appropriate. Specimens for bacterial or viral cultures or viral antigen detection can be submitted. A complete blood cell count may support the diagnosis of infection

Box 120.3. What to Ask

Vomiting

- What is the nature of the vomiting (eg, projectile, bilious, non-bilious)?
- How long has the child been vomiting?
- Are any symptoms, such as fever, diarrhea, dizziness, or lethargy, associated with the vomiting?
- What is the relationship of the vomiting to meals?
- Does the vomiting occur at night, indicating possible hiatal hernia and gastroesophageal reflux?
- Is there a family history of migraine headache?
- Is the child taking any medications?
- Have any measures been taken to relieve the vomiting?

or reveal signs of anemia. In breastfed neonates and infants, vomited blood should be evaluated using the Apt test to determine whether it came from the mother or infant.

Electrolytes should be obtained in infants or children with a history of significant vomiting and may confirm dehydration, acid-base imbalance, or electrolyte disturbance. Infants with pyloric stenosis who vomit stomach contents typically develop a hypochloremic-hypokalemic metabolic alkalosis, although symptoms must be present for 3 weeks for this disturbance to be noted. Currently, infants with pyloric stenosis are diagnosed earlier in the course of their illness using ultrasonography, and only a mild metabolic acidosis may be seen. A urinalysis also may show evidence of dehydration as well as signs of a UTI. Tests for inborn errors of metabolism, such as urine for acid analysis, are appropriate if this is suspected.

Imaging Studies

Radiographic procedures, such as esophagography or an upper GI series, are the procedures of choice for the diagnosis of esophageal and duodenal atresia and intestinal malrotation. An abdominal ultrasound is most effective in the diagnosis of pyloric stenosis or intussusception. A flat plate of the abdomen may show stomach distention, a double bubble sign (ie, air in the stomach and duodenum), or a paucity of intestinal air in cases of high-level obstruction. Consultation with a pediatric gastroenterologist may lead to additional diagnostic tests, such as endoscopic evaluation, 24- to 48-hour esophageal pH, or combined esophageal pH and impedance monitoring and upper GI endoscopy.

Management

The initial step in the management of vomiting in infants or children is to ensure adequate hydration and integrity of the cardiovascular bed. This may require the administration of intravenous fluids. Oral rehydration is the mainstay of therapy in infants and children whose vomiting is related to gastroenteritis. Small, frequent feedings with clear fluids are better tolerated than large, infrequent feedings, although the latter may be necessary in infants with diarrhea because each feeding may result in a bowel movement. Antiemetics such as phenothiazines are discouraged in children because of the high incidence of side effects, including dystonic posturing. Drugs commonly used in pediatric practice include antihistamines, dopamine D_2, and serotonin 5-HT3 receptor antagonists. Oral ondansetron hydrochloride is frequently used as a single dose to manage the vomiting seen in acute viral gastroenteritis in the pediatric emergency department or as repeated doses for hospitalized children with other conditions associated with vomiting.

Further management depends on the diagnosis. Bacterial infections should be treated with the appropriate antibiotics. Surgical conditions, such as pyloric stenosis or intussusception, should be managed urgently. Inborn errors of metabolism require consultation with a geneticist and dietary manipulation. Congenital adrenal hyperplasia should be managed in consultation with an endocrinologist. This condition necessitates replacement hormonal therapy.

Prognosis

Most cases of acute vomiting resolve spontaneously or are readily managed once the underlying condition is diagnosed. The overall prognosis is, therefore, quite good.

Protracted vomiting may result in starvation and FTT, however. Severe vomiting may cause tears in the esophagus and lead to hematemesis (Mallory-Weiss syndrome). Obstructive causes of vomiting in infants respond to surgical intervention.

CASE RESOLUTION

Bilious vomiting in a previously healthy infant is the warning sign of midgut volvulus and intestinal malrotation. It is a medical emergency due to high risk of extensive small bowel necrosis, which can lead to short bowel syndrome and even death. A prompt fluid resuscitation and urgent upper GI series or Doppler ultrasonography are mandatory to confirm the diagnosis and prepare the child for urgent surgery.

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CHAPTER 121

Gastroesophageal Reflux

George Gershman, MD

CASE STUDY

A 9-year-old boy reports frequent episodes of epigastric pain right after eating. The pain is associated with nausea and infrequent vomiting. The pain is described as dull and lasts less than 15 to 20 minutes. The patient also reports a burning sensation in his chest after eating and a cough at night. The patient lacks energy, and his voice is hoarse in the morning. There is no history of dysphagia, odynophagia, or weight loss. The physical examination is normal.

Questions

1. What are the characteristics of gastroesophageal reflux?
2. What is the difference between gastroesophageal reflux and gastroesophageal reflux disease?
3. What groups of children are at risk for gastroesophageal reflux disease?
4. What is the appropriate workup for an infant with suspected gastroesophageal reflux disease?
5. What is the appropriate management of infants and children with gastroesophageal reflux and gastroesophageal reflux disease?
6. What is the natural history of gastroesophageal reflux in children?

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus. It is a normal physiological process that occurs in healthy children and adults. Most episodes of reflux in healthy individuals are brief and asymptomatic and are rarely accompanied by *regurgitation,* defined as passage of gastric fluid into the pharynx or mouth. In otherwise healthy, thriving infants, GER is often associated with effortless expulsion of refluxate from the mouth; the condition is colloquially known as spitting up. Those infants fall into the category of "happy spitters."

In contrast with uncomplicated GER, symptomatic GER is defined as GER disease (GERD) and induces conditions such as esophagitis, failure to thrive, and aspiration pneumonia. While GER may require only anticipatory guidance and monitoring, GERD necessitates further evaluation and medical therapy. Thus, although GER could be a sign of GERD, it is important to distinguish these 2 entities for proper patient care.

Epidemiology

Gastroesophageal reflux is very common in infants; at least one-half of healthy infants experience some degree of GER. Most infants with GER or GERD who are brought in for medical care became symptomatic before 6 months of age. Regurgitation occurs at least once daily in one-half of infants younger than 3 months and in nearly two-thirds of infants by 4 months. The frequency and volume of spit-up decrease after age 7 to 8 months, when infants are upright for more of the day. By 12 months of age, only 5% of infants will remain symptomatic. By 18 months of age, most infants become asymptomatic.

Little is known about the prevalence of GERD in children and adolescents. A cross-sectional observational study in more than 10,000 children and adolescents (mean age 3.8 ± 5.6 years) in France revealed the prevalence of GERD as 6%. One retrospective study in the United States showed that 5% to 8% of children and adolescents suffered from weekly symptoms of GERD.

Available data suggest that children who were diagnosed with GERD at 5 years or older have a high prevalence of GERD symptoms in adolescence and as young adults. A small retrospective study of adults who had been diagnosed with GERD in infancy or childhood showed increased symptoms of GERD in those who had a history of GERD in childhood but not in infancy.

High-risk Groups

Patients with neurological disorders have an increased prevalence of GERD. Management of these individuals requires a more aggressive approach. Individuals with neurological impairments are more likely to have esophagitis or aspiration. Infants who have undergone repair of esophageal atresia also have more severe disease, with at least one-half requiring anti-reflux surgery. Chronic respiratory disease, such as cystic fibrosis, is associated with GERD. Gastroesophageal reflux disease is described in two-thirds of patients with asthma, but this association is controversial. It is not clear whether the altered physiology of these diseases causes reflux or if reflux exacerbates the pulmonary dysfunction. Similar triggers for asthma and GERD are described, so it may be that they coexist and are unrelated. Studies with intraluminal impedance monitoring (see the Evaluation section) show that nonacid reflux occurs frequently in patients with asthma. This helps explain the lack of success of therapy aimed at acid suppression in this group of patients.

Clinical Presentation

The most frequent presentation for infants with GER is recurrent non-forceful and small volume emeses (Box 121.1). Vomiting typically occurs after feeding and does not seem to disturb the patient. Some parents report a link between fussiness and crying with feeding, but this is not reproducible in trials comparing symptoms with pH studies. Additional symptoms, such as poor weight gain, anemia, or swallowing difficulties, could be linked to GERD. Sandifer syndrome is a rare presentation of GERD in infants, with characteristic paroxysmal movements involving spasmodic torticollis and dystonia. Nodding and rotation of the head, neck extension, gurgling, writhing movements of the limbs, and severe hypotonia can also be witnessed. Infants and children can develop extraesophageal manifestations of GERD such as nighttime cough, sleep apnea, wheezing, and recurrent pneumonia. Children older than 8 years and adolescents may have symptoms of adult-type GERD, such as frequent heartburn, chest and abdominal pain, and dysphagia.

Pathophysiology

Gastroesophageal reflux occurs when intra-abdominal pressure surpasses intrathoracic pressure. There are 3 main preventive barriers to GER: lower esophageal sphincter (LES), the crus of the diaphragm, and the intra-abdominal esophagus. A contracted LES generates a pressure gradient of 8 to 30 mm Hg between the esophagus and the stomach. The LES relaxes during swallowing, allowing a food bolus to enter the stomach. The skeletal muscle of the crus diaphragm contracts during inspiration or straining, augmenting the pressure of the LES. Contraction of the intra-abdominal esophagus in response to rising of intra-abdominal pressure adds to GER preventive forces.

Most episodes of GER occur during transient esophageal relaxation of LES that is not related to swallowing or straining. Transient esophageal relaxation of LES is considered to be a venting mechanism of the distended stomach and is manifested by belching in typical individuals. Transient esophageal relaxation of LES occurs up to 6 times per hour in typical adults, more frequently with gastric distension after meals, and rarely at night. In children, including preterm and term infants, transient esophageal relaxation of LES is responsible for most GER. Transient esophageal relaxation of LES is mediated by a brain stem reflex involving the vagal nerve and release of nitric oxide. Consumption of a large quantity of milk, poor compliance of the stomach, and a relatively short esophagus of a rapidly growing infant leads to frequent effortless regurgitation of gastric fluid into the esophagus. Posterior location of the gastroesophageal junction in the supine position and raised intra-abdominal pressure when the infant is resting in a car safety seat also facilitate regurgitation.

Transient esophageal relaxation of LES that is too frequent or prolonged exposes the esophageal mucosa to noxious material. Swallowed saliva and coordinated esophageal peristalsis neutralize gastric fluid within the esophagus and sweeps the fluid into the stomach. Inflammation of the esophagus may disrupt this process by decreasing peristaltic activity. Lack of mucus secretion by the esophageal mucosa and poor esophageal clearance increase the risk of esophagitis by exposing the esophageal mucosa to hydrochloric acid, pepsin, bile acids, and pancreatic enzymes. In contrast, frequent feedings with large volume of human milk or formula neutralize gastric acidity and decrease caustic damage of the esophagus in infants.

Before food leaves the esophagus, the stomach must be ready to accept it. The gastric fundus normally relaxes without an increase in pressure. Dysfunction of this fundic accommodation or delay in gastric emptying can increase pressure in the stomach and exacerbate GER.

Box 121.1. Diagnosis of Gastroesophageal Reflux Disease in the Pediatric Patient

Presenting Signs and Symptoms

- Regurgitation
- Vomiting
- Fussiness or sleep disturbance
- Poor weight gain
- Hematemesis or anemia
- Odynophagia or dysphagia
- Asthma/apnea/aspiration

Differential Diagnosis

A diverse group of symptoms, each with its own list of potential diagnoses, are associated with reflux disease. Regurgitation and vomiting are the most commonly reported symptoms. Many of the causes of vomiting in the newborn can be separated from reflux with a history and physical examination (Box 121.2). Forceful, bilious, or bloody emesis is not typical of reflux. Fussiness and crying are nonspecific symptoms with etiologies ranging from infantile colic to meningitis. Eosinophilic esophagitis (EoE) should be considered in toddlers and children with recurrent emesis and atopic dermatitis, food allergy, or asthma and older children and adolescents with dysphagia. Children with EoE may also experience recurrent food impaction in the esophagus. The primary therapy for EoE focuses on dietary manipulation and the elimination of identified foods to which the child is allergic.

Evaluation

Infants who fit into the definition of happy spitter (normal appearing, thriving, with recurrent emesis) do not require any diagnostic workup. It is important to reassure parents or guardians and encourage proper feeding technique. However, the presence of red flag symptoms, such as bilious vomiting, poor weight gain, food avoidance, chronic cough, unexplained anemia, or significant chest or abdominal pain, should prompt thorough diagnostic evaluation.

History

Targeted questions about the timing and volume of feedings and their relationship to regurgitation can help build the case for reflux. Specific attention should be paid to respiratory symptoms such as nighttime cough or previous episodes of pneumonia. Difficulties with feeding and swallowing should be outlined carefully. Gagging or dysphagia with different consistencies of food should be noted. Family history of reflux, especially as an

Box 121.2. Common Non-reflux Causes of Vomiting

Infections
- Sepsis
- Meningitis
- Urinary tract infection
- Otitis media

Obstruction
- Pyloric stenosis
- Malrotation
- Intussusception

Gastrointestinal
- Eosinophilic esophagitis
- Peptic ulcer disease
- Achalasia
- Gastroparesis
- Gastroenteritis
- Gall bladder disease
- Pancreatitis
- Celiac disease
- Pill esophagitis
- Crohn disease

Metabolic/Endocrine
- Galactosemia
- Fructose intolerance
- Urea cycle defects
- Diabetic ketoacidosis

Toxic
- Lead poisoning

Neurological
- Hydrocephalus and shunt malfunctions
- Subdural hematoma
- Intracranial hemorrhage
- Tumors
- Migraine

Allergic
- Dietary protein intolerance

Respiratory
- Post-tussive emesis
- Pneumonia

Renal
- Obstructive uropathy
- Renal insufficiency

Cardiac
- Congestive heart failure

Other
- Overfeeding
- Self-induced vomiting

Other (Seen in Adolescents)
- Recreational drugs
- Alcohol
- Pregnancy

infant, may be helpful. Clinical questionnaires, including the Infant Gastroesophageal Reflux Questionnaire, have been validated but do not predict prognosis or severity. They are more useful in the research setting.

Physical Examination

A full physical examination should be performed, including an observance of feeding. Neurological deficits or delay should be noted. The abdomen should be carefully palpated for masses or distension. Growth parameters should be reviewed longitudinally, and the child's body habitus, particularly the amount of subcutaneous tissue, should be noted.

Laboratory Tests

Most patients with reflux will need no laboratory testing. Urinalysis and culture are reasonable tests in an infant with sudden onset of emesis. Children with large-volume emesis or weight loss should be assessed for acidosis or other electrolyte abnormalities. Markers of kidney and liver function are reasonable to obtain. Anemia workup should be initiated in a child who is pale, irritable, and undernourished.

Intraesophageal pH Monitoring

Currently, measurement of the intraesophageal pH for periods of 24 to 48 hours is considered the standard for the diagnosis of GERD. This is performed by placing a catheter trans-nasally into the distal esophagus to measure the intraluminal pH as the patient records the symptoms, such as cough and pain. Meals are also recorded. Monitoring of pH can be performed safely in all age groups, and certain parameters of this procedure correlate with esophagitis. Such monitoring does not detect nonacid reflux, however, making its utility in linking respiratory disease to GERD questionable. It may be combined with multichannel sleep studies to investigate apnea or nighttime symptoms. A wireless device that attaches to the esophageal mucosa has been used in children. The device can be placed with or without endoscopy, but the size of the capsule may prohibit its use in smaller children.

Combined Multiple Intraluminal Impedance and pH Monitoring

Impedance monitoring is being used more often to diagnose GER in children. This technology involves the placement of a catheter trans-nasally into the esophagus for measurement of ionic conductivity, which is low when the esophagus is empty and increases when it contains liquid. The catheter has multiple sensors that can detect the direction of liquid flow. Decrease of intraesophageal impedance by liquids moving from the distal sensors upward determines reflux. The addition of a pH sensor to the distal end of the catheter allows the defining of reflux as acid or nonacid. It is superior to pH monitoring alone for evaluation of the temporal relation between symptoms and GER. This study is equally effective in both breastfed and formula-fed infants because it eliminates the buffering effect of human milk or formula on gastric acid to detect nonacid reflux.

Upper Gastrointestinal Series

Upper gastrointestinal radiography is not useful for the diagnosis of GERD because of low sensitivity and specificity. It should be used only to confirm or rule out anatomical abnormalities such as malrotation, esophageal or intestinal webs, or hiatal hernia that may cause symptoms similar to those of GERD.

Nuclear Scintigraphy

The test is based on administration of an age-appropriate feeding of technetium-labeled food. It is designed to assess gastric emptying and detect the reflux of a tracer in the esophagus. The standards for interpretation of this test are poorly established. According to limited published literature, scintigraphy may have a role in the diagnosis of pulmonary aspiration in patients with chronic and refractory respiratory symptoms. A negative test result does not rule out possible pulmonary aspiration of refluxed material. Gastric emptying studies by themselves do not confirm the diagnosis of GERD and are recommended only in individuals with symptoms of gastric retention. Nuclear scintigraphy is not recommended for the routine evaluation of pediatric patients with suspected GERD.

Endoscopy With Biopsy

Endoscopy of the upper gastrointestinal tract allows direct visualization of the esophagus and attainment of mucosal biopsies. The presence and severity of esophagitis can be documented. Other disease processes, including infection, EoE, and Crohn, can be detected. Biopsies should always be taken, even in the absence of macroscopic findings.

Management

Infants who are thriving with no symptoms other than regurgitation or vomiting will benefit primarily from alleviation of parental anxiety. Discussion involving the normal course and benign nature of GER may be all that is required. The infant should be followed by a pediatrician until the resolution of symptoms. Referral to a pediatric gastroenterologist should be considered when GERD is suspected.

Lifestyle Changes

Life in recumbence has its disadvantages for infants, namely allowing the esophagus and stomach to reside at the same level. This concept has led to the use of positioning in infants. Multiple positions are used, including prone, prone at a 30° angle, or supine at a 30° angle. The only proven position seems to be prone, which has been associated with an increased rate of sudden unexpected infant death (SUID). The health professional must balance the risk of GERD with that of SUID in the individual patient. The 30° supine position does not seem to be more effective in decreasing reflux than the flat supine position, but there is conflicting evidence on this point.

Infants with reflux are often put through "formula roulette." Cow's milk or soy-based formulas are used, and some infants progress to other formulas, such as hypoallergenic, predigested, or elemental types. This is more likely in the patient with a family history of atopy. Nearly half of infants intolerant of milk protein will also exhibit symptoms with soy; thus, protein hydrolysate formulations may be of more use. There is no indication for lactose-free cow's milk formulas in this patient population. Rice cereal may be used as a thickening agent. This does not change findings on esophageal pH monitoring, but it may decrease the frequency of regurgitation. Patients with poor weight gain will benefit from the increased caloric density of the thickened formula. One tablespoon of rice cereal per 2 oz of formula will increase the content from 20 to 27 cal/oz. Increasing amounts of rice cereal will increase the viscosity and caloric density, but this also increases osmolarity. Excessively concentrated formulas may worsen vomiting. Nipples used with thickened formula will need to be tailored by crosscutting, but this may lead to increases in coughing or gagging. Formulas containing commercial "anti-regurgitant" agents are now available. Although no more effective than rice cereal for regurgitation, they do not increase the caloric density and may require less energy to pull from the nipple. This must be balanced with the unknown long-term risks of these newer ingredients as well as the increased cost.

Environmental and dietary factors have been studied in the older child and teenager. Currently, only caffeine, chocolate, and spicy foods that provoke symptoms should be avoided. Obesity and exposure to tobacco smoke have also been implicated.

Medications

The pharmacological agents used in reflux disease are felt to be safe and, therefore, are sometimes used empirically without diagnostic confirmation (Table 121.1). Although this approach may be useful in adolescents for up to 4 weeks, it should be used with caution in infants or young children. There is emerging evidence of harm caused by acid suppression, especially proton pump inhibitors (PPIs), although acid suppression is the mainstay of treatment. The goal is to reduce exposure of the esophagus to acid. The 3 main types of drugs that can be used are antacids, H_2-receptor antagonists, and PPIs. The only clinically effective antacids are those that contain aluminum, which has been associated with bone and nervous system toxicity, especially in infants. H_2-receptor antagonists inhibit acid production in the gastric parietal cell. They are effective in the healing of esophagitis; however, tachyphylaxis has been seen as early as 1 week after initiation. Further complicating this class of medications are adverse effects, such as fussiness, that may be mistaken for reflux symptoms. Cimetidine and famotidine have the most evidence for effective and safe use in pediatrics.

Proton pump inhibitors bond and deactivate hydrogen, irreversibly inhibiting hydrogen potassium adenosine triphosphatase, the final pathway of gastric acid. Proton pump inhibitors should be taken 30 minutes prior to a meal so that the drug is in the bloodstream in the largest concentration at mealtime. Omeprazole, lansoprazole, and esomeprazole magnesium have been studied in children. No PPI has been approved for use in infants younger than 1 year. Proton pump inhibitors may be used as the initial drug or following failure of H_2-receptor antagonists.

There are emerging studies in children and adults showing adverse effects from long-term acid suppression. Up to 14% of patients can have adverse effects of headache, diarrhea, constipation, or nausea. Increased rates of community-acquired pneumonia, gastroenteritis, and necrotizing enterocolitis have been described. Adult studies have shown increased hip fractures and vitamin B_{12} deficiency, suggesting malabsorption secondary to hypochlorhydria, but these have not been reproduced in children. More studies are needed to understand the significance of these adverse effects. Currently, the efficacy of empiric therapy with PPI in children is not established, and empiric therapy should be used with caution, especially in young children. Administration of long-term acid suppression without a diagnosis is inadvisable. When acid suppression is required, the smallest effective dose should be used.

Prokinetic agents are indicated in the patient with evidence of delayed gastric emptying. Cisapride, a mixed serotonergic agent, was the model drug for this class. It has been shown to improve reflux symptoms and pH parameters in infants. However, it has been associated with QT prolongation and arrhythmia with some deaths. The use of cisapride has been severely restricted since the

Table 121.1. Pharmacological Agents Used for Reflux Disease

Drug	*Pediatric Dose*	*Adverse Effects*
Cimetidine	20–40 mg/kg/day, divided 3–4 doses per day	Hypotension, gynecomastia, reduced hepatic metabolism of other drugs, neutropenia, agranulocytosis, thrombocytopenia
Famotidine	0.5–1 mg/kg/day as a single dose or divided into 2 doses	Headache, dizziness, constipation, diarrhea
Omeprazole	0.7–3.3 mg/kg/day divided into 2 doses	Headache, diarrhea, abdominal pain, nausea, rash, vitamin B_{12} deficiency, constipation
Lansoprazole	15 mg (weight ≤30 kg) 30 mg (weight >30 kg)	Headache, nausea, constipation, diarrhea, abdominal pain, proteinuria, hypotension, elevated transaminases
Metoclopramide	0.1 mg/kg/dose 4 times per day before meals	Drowsiness, restlessness, dystonia, gynecomastia, galactorrhea
Erythromycin	3–5 mg/kg/dose 3–4 times per day before meals	Diarrhea, vomiting, cramps, antibiotic effect, pyloric stenosis

year 2000. Other drugs in the group are less likely to improve reflux but are still widely used. Metoclopramide also has mixed serotonergic effects, in addition to antidopaminergic and cholinomimetic actions. Adverse effects, including central nervous system complications, limit the use of this drug; it now carries a black box warning from the US Food and Drug Administration. Erythromycin is a motilin receptor agonist that is also used less commonly in GERD. There is evidence that its use in pregnancy or young infants may increase the risk of pyloric stenosis. Many interactions have been seen with this macrolide antibiotic, which also limits its use. Thus, potential adverse effects of currently available prokinetic agents outweigh the potential benefits of these medications for treatment of GERD.

Buffering agents, alginate, and sucralfate are useful on demand for occasional heartburn. Chronic use of buffering agents or sodium alginate is not recommended for GERD because some have absorbable components that may have adverse effects with long-term use. Special caution is required in infants.

Anti-reflux Procedures

Patients who continue to have reflux on maximum medical therapy, or those who have serious extraesophageal manifestations, such as recurrent aspiration, should be considered for surgery. Patients requiring long-term drug therapy may also be selected for surgery. The most popular procedure is the Nissen fundoplication. The laparoscopic approach to fundoplication is used widely and entails a full wrap of the fundus of the stomach around the esophagus to increase LES tone and create a more acute angle of His. More than 90% of patients remain symptom-free up to 11 years postoperatively. Complications, including gas bloat, dumping syndrome, and dysphagia, are reported at variable frequencies. Failure rates are higher in children who have neurological impairment and those with esophageal atresia repair. There are several other fundoplication procedures that have variable degrees of wrapping.

Significant delay in gastric emptying may require an additional surgical procedure at the gastric outlet. Pyloroplasty enhances the exit from the stomach. There is some concern that fundoplication itself results in accelerated gastric emptying and additive effects of pyloroplasty might result in dumping of gastric contents into the duodenum too rapidly, but this has not been shown to be a significant problem, and this procedure should be given strong consideration in infants or children with documented moderate or severe delayed gastric emptying.

Endoscopic anti-reflux procedures have mixed results in adults. The most studied and effective procedure is trans-oral incisionless fundoplication, which involves placing sutures through the gastroesophageal junction, pleating the mucosa and reinforcing LES. Pediatric experience with trans-oral incisionless fundoplication is limited to a few dozen cases. The preliminary results showed that the procedure is safe and efficacious in a highly selected group of older children and adolescents.

Prognosis

Complications arising from untreated GERD include esophagitis, Barrett syndrome, strictures, and esophageal adenocarcinoma and aspiration. However, most infants with GER have a more favorable outcome. Regurgitation resolves in most children by 18 months of age and is absent by 24 months of age in 98%. There is some evidence that a portion of patients who become asymptomatic will continue to have abnormal histology in the esophagus at follow-up endoscopy. Therefore, it is unclear if the disease process continues into later childhood. Future studies that follow infants with reflux longitudinally into adulthood will be of great benefit. There is much to be learned in the area of nonacid reflux and its role in respiratory disease as intraluminal impedance becomes more widely used.

Children with reflux symptoms that persist into later childhood have a worse prognosis. Patients with a history of esophageal atresia repair or severe neurological injury may have a poor prognosis, often requiring high-dose medication or anti-reflux surgery. They are more likely to experience complications of GERD.

CASE RESOLUTION

The patient has symptoms suggestive of GERD (ie, epigastric pain after eating associated with nausea, burning sensation in his chest, and nocturnal cough). Consideration can be given to initiating medications such as H_2-receptor antagonists. Alternatively, an upper gastrointestinal endoscopy can be obtained to document the presence of reflux or other forms of esophagitis.

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CHAPTER 122

Gastrointestinal Bleeding

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CASE STUDY

A 5-year-old boy is evaluated for a history of hematemesis. The mother reports that her son experienced a sudden onset of vomiting of a large amount of blood. She denies that her son picks his nose or has had recent trauma. The boy's past medical history is significant for a double volume exchange blood transfusion as an infant. The boy has no history of recent upper respiratory infection, chronic cough, recurrent vomiting, abdominal pain, weight loss, or jaundice. He takes no medications. The family has no pets and has not traveled recently.

On physical examination, the boy is pale, frightened, and anxious. His temperature is normal, pulse is 120 beats per minute, blood pressure is 90/60 mm Hg, and respirations are 25 breaths per minute. Weight and height are at the 75th percentile for his age. The sclerae are white and the neck is supple, and there is no lymphadenopathy. Lung sounds are clear, heart sounds are normal, and the abdomen is soft, slightly distended, and nontender, with normal bowel sounds. The liver is not palpable, but the spleen is enlarged, with the tip palpable approximately 6 cm below the left costal margin. There is no evidence of ascites or caput medusae. The boy's skin is pale without rash or bruises. His extremities are cold, with capillary refill of more than 3 seconds. The results of a complete blood cell count and blood chemistry, including liver function test, are normal except for mild thrombocytopenia. A prothrombin international normalized ratio and partial thromboplastin time determination yield typical results.

Questions

1. What is a proper means of assessing children with gastrointestinal bleeding?
2. What are the specific characteristics of upper and lower gastrointestinal tract bleeding?
3. What age-related conditions account for upper and lower gastrointestinal tract bleeding in children?
4. What is the appropriate approach to the child with gastrointestinal bleeding?

Bleeding from the gastrointestinal (GI) tract in infants and children is always stressful and frightening for patients and their parents. Diagnosis and management can also be challenging for a physician, especially if bleeding is severe, although fortunately, encountering life-threatening GI bleeding in pediatric practice is rare. When it does occur, acute GI bleeding in children is a true medical emergency, associated with significant morbidity and mortality, even in high-income countries. A recent retrospective analysis of acute GI bleeding in patients admitted to 47 pediatric tertiary centers in the United States (data extracted from Pediatric Health Information System Database) revealed a mortality of almost 0.4% and 3% in children with the primary and secondary diagnosis of acute GI bleeding, respectively. Therefore, a pediatrician or emergency department (ED) physician should be prepared to initiate effective resuscitation and a diagnostic workup focusing on common age-specific causes of GI bleeding. The primary goal of this approach is a reduction of morbidity associated with significant hemorrhage.

Epidemiology

Upper GI bleeding is uncommon in infants and children, although the exact incidence is unknown. Clinical experience suggests that the incidence in children is significantly less than in adults. This assertion is supported indirectly by epidemiological data from the United Kingdom and United States, which indicate that the incidence of upper GI bleeding in adults younger than 29 years is approximately 18 to 23 per 100,000 adults per year, which is almost 4 to 5 times lower than among older age groups. The risk of upper GI bleeding is relatively high (between 6% and 25%) in pediatric patients admitted to pediatric intensive care units. Clinically significant upper GI bleeding, defined as a drop in hemoglobin level of 2.0 g/dL; indication for blood transfusion; emergent endoscopy; or surgery has been documented in 4% of children presenting to an ED with hematemesis.

Low GI bleeding is quite common in pediatric practice. However, the epidemiology of this problem is not well established. In 1 study, rectal bleeding was the presenting symptom in 0.3% of all visits to a tertiary ED during a 10-month period.

Clinical Presentation

Bleeding into the GI tract can present as hematemesis, melena, occult bleeding, or hematochezia.

Hematemesis is vomiting of bright-red "fresh" blood or coffee-ground (dark-brown) "old" blood exposed to hydrochloric acid. Usually, hematemesis reflects acute bleeding from the esophagus, stomach, or proximal duodenum. Swallowed maternal blood in neonates and epistaxis in older children should be ruled out to avoid unnecessary invasive procedures.

Melena is characterized as liquid, coal-black, shiny, sticky, tarry, foul-smelling stool. It suggests bleeding from the upper GI tract. Occasionally, bleeding from the ileum can be associated with melena. However, in this case, the stool is black but not tarry. Melena suggests a minimum loss of 50 to 100 mL of blood in adults (1%–2% of total blood volume) or 2% of the total blood volume in children. Stool may remain black or tarry for a few days after massive hemorrhage, even though active bleeding has ceased.

Occult bleeding is defined as the presence of a non-visible quantity of blood in stool. It usually occurs as chronic, recurrent losses of small amounts of blood, which can lead to severe microcytic anemia. The most commonly used technique for detection of blood in stool is a fecal occult blood test. This test is based on the chemical reaction of a dye (guaiac) with peroxidase-containing substances and hydrogen peroxide. It is not specific for the presence of blood (hemoglobin) in stool. False-positive results could be secondary to peroxidase activity in food products such as cantaloupes, radishes, bean sprouts, cauliflower, broccoli, grapes, and red meat or iron preparations. False-negative results are associated with prolonged colonic transient time and bacterial degradation of hemoglobin to porphyrin, which does not have peroxidase activity.

Currently, a fecal immunochemical test is available for detection of blood in stool based on labeling of human hemoglobin by specific antibodies. The test does not require a special diet. It is more specific for the detection of bleeding from the colon due to enzymatic digestion of the hemoglobin from the upper GI tract.

Hematochezia is the passage of bright-red or maroon-colored blood from the rectum. This may be pure blood, bloody diarrhea, or blood mixed with stool. Typically, it is a sign of lower GI bleeding from the distal colon or, less frequently, from the right colon or distal ileum. Rarely, hematochezia may occur in children with massive bleeding from the duodenum.

Pathophysiology

Compensatory responses to acute bleeding restore depleted intravascular volume, maintain a normal cardiac output and adequate oxygenation of vital organs (ie, brain, heart, lungs, adrenal gland), and mobilize internal energy stores.

Two parameters determine the degree of compensation: volume of blood loss and velocity of bleeding.

Mild Blood Loss (<15% of Circulatory Volume) or Class 1 Bleeding

Relatively slow blood loss of less than 15% of the total blood volume triggers redistribution of depot blood from the venous system to the systemic circulation and a shift of extracellular fluids into the vascular space. Adequate cardiac output without changes in heart rate and blood pressure is maintained, and there are no hemodynamic abnormalities. However, a rapid blood loss (even <10% of blood volume) may compromise cardiac output and trigger tachycardia and other compensatory mechanisms to restore normal blood circulation.

Moderate Blood Loss (Between 15% and 30% of Circulating Volume) or Class 2 Bleeding

Blood loss of more than 15% of the total blood volume leads to *tachycardia,* an increased systemic vascular resistance caused by activation of the sympathetic nervous system and hypothalamic-pituitary-adrenomedullary axis. In children, cardiac output depends on heart rate rather than stroke volume due to a smaller ventricular mass. With hemorrhage, tachycardia is the principal mechanism for maintenance of an adequate cardiac output in pediatric patients; however, prolonged tachycardia increases myocardial oxygen demand and decreases diastolic-dependent coronary perfusion. This eventually leads to cardiovascular decompensation if fluid resuscitation is delayed or insufficient.

Normal blood pressure and adequate perfusion of vital organs in children with moderate bleeding is maintained by increased systemic vascular resistance and redistribution of blood from skin, muscle, splanchnic organs, and kidney to the brain, heart, lungs, and adrenal gland due to local production of adenosine, nitric oxide, and prostaglandins. Therefore, blood pressure is a poor indicator of cardiovascular homeostasis in children with moderate GI bleeding. In contrast, persistent tachycardia is the red flag of pending cardiovascular collapse.

Severe Blood Loss (>30% of Circulating Volume) or Class 3 Bleeding

Failure of compensatory mechanisms and decreased cardiac output lead to hypotension and tissue hypoxia. Compensatory tachypnea contributes to respiratory alkalosis in the initial phase of severe bleeding. Tissue hypoxia compromises mitochondria functional capacity to generate energy as adenosine triphosphate. This leads to metabolic acidosis due to excessive production of lactic acid and cellular death.

Hypoperfusion of the kidney causes acute spasm of the preglomerular arterioles and acute tubular necrosis and renal failure. Hypoxia and excessive cytokine production can induce liver failure—sudden onset of jaundice due to hepatocellular necrosis, elevation of transaminases, coagulopathy, hypoglycemia, and encephalopathy. Myocardial ischemia is a common consequence of severe bleeding. Sepsis, thrombotic microangiopathy, and a systemic inflammatory response syndrome may occur in the late stages of uncontrolled or inadequately treated severe hemorrhage.

Evaluation

The initial assessment of the child with suspected GI bleeding should be focused on signs of hemodynamic instability and clues for the etiology of bleeding. Four major questions must be answered promptly: Is the patient stable? Is the bleeding real? What is the source of the bleeding? What is the best treatment option?

The first and most important step in the initial assessment of the child with suspected GI bleeding is recognition of hemodynamic instability (Box 122.1).

Box 122.1. Procedural Management of Gastrointestinal Bleeding

Endoscopic Hemostasis of Non-varicose Bleeding

Indications

- Active bleeding from a gastric or duodenal ulcer
- Stigmata of recent bleeding: a non-bleeding visible vessel in the ulcer base and a densely adherent clot
- Bleeding arteriovenous malformation
- Bleeding after polypectomy

Methods

- Injection of vasoconstrictive agent
- Thermal coagulation
  - — Bipolar coagulation
  - — Heater probes
  - — Argon plasma coagulation device
- Metal clips

Endoscopic Hemostasis of Varicose Bleeding

Indications

- Active bleeding from esophageal or gastric varices
- History of bleeding secondary to portal hypertension
- Failure of shunting procedure

Techniques

- Sclerotherapy
- Endoscopic varicose ligation

Polypectomy

Indication

- Juvenile polyps <3 cm
- Multiple polyps <2 cm

A prompt assessment of estimated blood loss and the degree of hemodynamic instability should be done using objective criteria, such as mental status, skin color, capillary refill, pulse, blood pressure, and orthostatic maneuvers (Table 122.1). Special attention should be focused on tachycardia and narrowed pulse pressure, which are the earliest signs of impending shock. Hypotension usually occurs in the late phase of shock in children and is an ominous finding. The value of the initial hematocrit may not accurately reflect the severity of blood loss. First, the hematocrit does not fall immediately with hemorrhage due to proportionate reductions of plasma and red cell volumes. Second, the hematocrit begins to fall due to compensatory restoration of the intravascular volume by the shift of extravascular fluids into the vascular bed. This process begins shortly after the onset of bleeding; however, it is not complete for 24 to 72 hours. At this point, plasma volume is larger than normal, and the hematocrit reaches its true nadir, assuming that bleeding has stopped.

Differential Diagnosis

The 3 essential components of the diagnosis of GI bleeding are confirmation that bleeding is real, allocation of the bleeding area to the upper versus lower GI tract, and detection of the specific cause of bleeding.

Table 122.1. Clinical Manifestations of Gastrointestinal Bleeding According to Blood Loss Volume

	Blood Loss		
Symptoms and Signs	*<15%*	*15%–30%*	*> 30%*
Normal appearance	+	–	–
Anxiety	–	+	+
Disorientation	–	–	+
Lethargy	–	–	+
Tachycardia	–	++	+
Pallor	–	+	++
Livedo reticularis	–	+	++
Cold extremities	–	+	+
Capillary refill >2 seconds	–	+	+
Hypotension	–	–	+
Narrowed pulse pressure	–	+	+
Elevated diastolic pressure	–	+	–
Low diastolic pressure	–	–	+

Abbreviations: –, absent; +, present, mild; ++ present, moderate.

Red staining of emesis or stool can be induced by cranberries, cranberry juice, cherries, strawberries, beets, tomatoes, candies, amoxicillin, phenytoin, red-colored rehydrating drinks (eg, Gatorade, Powerade), and rifampin. Bismuth preparations, activated charcoal, iron, spinach, blueberries, and licorice can simulate bleeding by staining emesis and coloring stool black. An appropriate history, a normal physical examination, and guaiac-negative stool are sufficient to rule out a true bleeding episode.

It is important to remember that hematemesis or melena can be secondary to epistaxis. History of recent tonsillectomy and adenoidectomy, nasal allergies, dry environment, or nose-picking habits increases the probability of epistaxis. Thorough examination of the nose and oropharynx can help to establish the correct diagnosis.

Detailed history and physical examination help narrow the diagnostic workup. For example, treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) is a risk factor for acute gastric ulcers and bleeding from the stomach. Jaundice, hepatomegaly, spider hemangiomas, prominent vessels of the abdominal wall, or ascites are the signs of chronic liver disease and are suggestive of portal hypertension. However, GI bleeding in a febrile child with hemodynamic instability and jaundice could be secondary to sepsis-related coagulopathy or acute liver failure.

Careful assessment of the perineum can reveal anal fissures, fistulas, or perianal inflammation.

If the source of bleeding is not obvious, the placement of a nasogastric tube is very useful. A tube with the largest bore tolerable should be placed for adequate gastric lavage. A 10F to 12F sump tube is a reasonable choice for small children; a 14F to 16F tube is reasonable for older patients. Room temperature saline is the optimal fluid for irrigation. Iced saline lavage is no longer recommended

because it compromises platelet function at the bleeding site and may induce hypothermia (especially in infants) with subsequent clinically significant arrhythmia. A bloody or coffee-ground aspirate indicates upper GI bleeding, if epistaxis was ruled out. The absence of blood in the stomach does not exclude upper GI bleeding because the source of hemorrhage can be in the duodenum. The presence of coffee-ground fluid in gastric aspirate, which promptly clears by gastric lavage, suggests that bleeding has stopped. Failure to obtain clear return on gastric lavage indicates ongoing bleeding.

Results of blood tests give some clues to the nature of bleeding. Low hemoglobin and hematocrit with normal mean corpuscular volume (MCV) are typical for acute blood loss. Elevated levels of blood urea nitrogen is suggestive of volume depletion and absorption of the blood proteins in the small intestine, which supports the diagnosis of upper GI bleeding. Very low hemoglobin, hematocrit, and MCV levels in a hemodynamically stable patient are consistent with chronic GI blood loss.

Knowledge of common causes of GI bleeding in an age-specific group of children helps with diagnostic strategy (Table 122.2).

In general, endoscopy is the method of choice for the diagnosis of the specific causes of acute and chronic GI bleeding related to mucosal and submucosal lesions of the GI tract. The choice of the particular type of endoscopic procedure is related to suspected pathology. Upper and lower GI endoscopy and enteroscopy are routine methods for diagnosis of diseases such as acute or peptic ulcers, esophagitis, gastritis, esophageal varices, vascular malformations, ulcerative colitis, Crohn disease, polyps, and other causes of GI bleeding. Capsule endoscopy is the minimally invasive method of endoscopic investigation of the entire small intestine. It is used for diagnosis of GI bleeding of obscure origin, usually after negative results of conventional endoscopic procedures.

Plain radiography and abdominal ultrasonography are useful for diagnosis of structural abnormalities such as intussusception, necrotizing enterocolitis, and malrotation.

Technetium Tc 99m pertechnetate scanning is indicated in children with suspected Meckel diverticulum. It is 85% sensitive and 95% specific.

The calculated rate of blood loss serves to guide the method to diagnose the source of hemorrhage. Angiography (rate ≥0.5 mL/minute), computed tomography angiography (0.35 mL/minute), and technetium-labeled red blood cell scanning (0.2 mL/minute) are alternatives to endoscopy for diagnosis of source of active GI bleeding.

These modalities should be considered when vascular anomalies or hemobilia are suspected.

Table 122.2. Common Causes of Gastrointestinal Bleeding in Children

Age	*Upper GI Bleeding*	*Lower GI Bleeding*
Neonates (0–30 days)	Swallowed maternal blood Stress ulcers/sepsis Hemorrhagic gastritis Hemorrhagic disease of the newborn	Necrotizing enterocolitis Midgut volvulus Congenital megacolon (Hirschsprung disease) Vascular malformation
Infants (30 days–6 months)	Cow's milk or soy protein allergy Esophagitis Prolapse gastropathy	Anal fissure Allergic proctitis or enterocolitis Intestinal lymphoid hyperplasia Intussusception
Infants and children (6 months–6 years)	Epistaxis Esophagitis Prolapse gastropathy Portal hypertension Drug-induced ulcers Gastritis Mallory-Weiss tear	Anal fissures Intussusception Meckel diverticulum Intestinal lymphoid hyperplasia Polyps Infectious colitis Hemolytic uremic syndrome Henoch-Schönlein purpura
Children and teenagers (7–18 years)	Epistaxis Drug-induced gastropathy and acute ulcers Peptic ulcer Esophagitis Gastritis Portal hypertension	Infectious colitis Ulcerative colitis Crohn disease Anal fissure Polyps

Abbreviation: GI, gastrointestinal.

Age-Associated Causes of GI Bleeding

Neonates

In healthy breastfed neonates and infants, hematemesis could be caused by swallowed maternal blood. In such cases, careful examination of maternal breast and areola can lead to correct diagnosis. In addition, the Apt test can be useful, especially in the first 3 to 4 weeks after birth, while concentration of fetal hemoglobin is still high. The test is based on the chemical reaction of adult hemoglobin with sodium hydroxide, which leads to a color change from bright red to yellow or crusty brown. Fetal hemoglobin is resistant to hydroxylation, and blood from the neonate remains bright red.

Acute gastric or duodenal ulcers should be suspected in neonates who are sick and preterm or who are septic or asphyxiated and full term, or in patients with intracerebral bleeding, increased intracranial pressure, congenital heart disease, respiratory failure, or hypoglycemia. The typical scenario includes sudden onset of hematemesis or melena and signs of hemodynamic instability. Occasionally, severe upper GI bleeding can occur in healthy full-term neonates within the first few days after birth.

Gastrointestinal bleeding is a common manifestation of necrotizing enterocolitis. The warning signs of necrotizing enterocolitis are abdominal distention, feeding intolerance with increased gastric residuals, mild diarrhea, hematochezia, or stool that tests positive for occult blood.

Plain radiographs can be diagnostic if they show pneumatosis intestinalis or gas in the portal vein.

Rare causes of GI bleeding in the first month after birth include Hirschsprung enterocolitis, midgut volvulus, duplication cyst, vascular malformation, and hemorrhagic disease of the newborn, particularly in breastfed neonates who did not receive vitamin K.

Infants Up to First 6 Months of Age

One of the leading causes of GI bleeding in infants younger than 6 months is cow's milk or soy protein allergy. The spectrum of symptoms includes recurrent vomiting, hematemesis, failure to thrive, and diarrhea with guaiac-positive stools or hematochezia.

Exclusively breastfeeding infants may develop similar symptoms on rare occasions. Elimination of cow's milk, eggs, peanuts, fish, and tree nuts from maternal diet may lead to resolution of allergic symptoms in the breastfeeding infant. For infants with persistent symptoms or whose mothers are unable to restrict their diet according to current recommendations and for formula-fed infants with cow's milk protein allergy, hypoallergenic (extensively hydrolyzed and free amino acid–based) formulas can be used to relieve the symptoms. Most infants with GI manifestations of cow's milk protein allergy will improve within the first 2 weeks of treatment.

An anal fissure is another common cause of bleeding in infants. The diagnosis is made by careful examination of the anus.

Intermittent rectal bleeding with streaks of frank blood mixed with normal-appearing stool can be secondary to intestinal lymphoid hyperplasia of the colon or terminal ileum. During endoscopy, multiple hemispheric smooth nodules of less than 4 mm can be found in clusters or diffusely throughout the GI tract. It is considered an excessive reaction of the GI tract lymphatic tissue (lymphoid follicles and Peyer patches) to food-related or other antigens. Spontaneous regression of lymphoid follicles is quite common. In addition to parental reassurance, an elimination diet for breastfeeding mothers is a reasonable initial treatment. Feeding with extensively hydrolyzed protein formula is the next therapeutic step. Corticosteroid therapy is restricted to infants with a severe form of this disease—recurrent abdominal pain, significant anemia, persistent rectal bleeding, diarrhea, and failure to thrive. In such cases, immunodeficiency has to be excluded.

Esophagitis should be suspected as a cause of bleeding in infants with a history of recurrent emesis and interrupted feeding patterns associated with crying, irritability, or arching. Patients with repaired esophageal atresia with or without tracheoesophageal fistula are at increased risk of severe reflux disease and esophagitis. Bleeding induced by esophagitis is usually recurrent and not intensive. The patients may have hematemesis with streaks of blood or guaiac-positive stool.

Infants or older children can develop minor bleeding due to prolapse of gastric mucosa into the esophagus through the gastroesophageal junction (prolapse gastropathy). This condition is manifested by recurrent emesis with food and appearance of flecks of denatured blood at the end of vomiting. The presence of large amounts of frank blood or clots at the end of recurrent emesis is suggestive of a more serious problem, such as Mallory-Weiss tear.

Infants and Children Younger Than 7 Years

Several diseases have a higher prevalence in this age group compared with other children.

The signs and symptoms of *portal hypertension* are a large-volume hematemesis, history of omphalitis secondary to catheterization of the umbilical vein, presence of splenomegaly or hepatosplenomegaly, and other stigmata of chronic liver disease, such as jaundice, spider angiomas, caput medusa, and ascites. Esophageal varices are the most common site of bleeding in children with intrahepatic-sinusoidal and extrahepatic-presinusoidal forms of portal hypertension. Two-thirds of children with portal hypertension will bleed before 5 years of age. The diagnosis is based on the presence of esophageal or gastric varices or hypertensive gastropathy during an upper GI endoscopy.

Intussusception, which is more common in the first 2 postnatal years, is strongly considered in infants and children with sudden onset of severe, cramping abdominal pain intercepted by pain-free episodes and currant jelly stools. A lead point is often present in children older than 2 years. Diagnosis is confirmed by ultrasonography (positive: "concentric circles" or the "target-shaped sign") or barium enema. Hydrostatic reduction of intussusceptions is successful in more than 90% of children.

Meckel diverticulum is the most common congenital anomaly in children. It is estimated that approximately 2% of infants have a remnant of the omphalomesenteric duct. However, fewer than 5% of children will develop complications, including GI bleeding. The predominant location of Meckel diverticulum is the distal ileum (40–60 cm above the ileocecal valve). Ectopic tissue is present in up to 80% of symptomatic patients. Gastric mucosa is the most common type of ectopia. The cause of bleeding is peptic ulceration at the junction of the ectopic gastric mucosa and normal ileum, the so-called marginal ulcer. Bleeding can be massive, but it may cease spontaneously secondary to contraction of the splanchnic vessels in response to hypovolemia. This phenomenon explains the intermittent nature of bleeding from Meckel diverticulum. Bleeding is usually painless but sometimes coincides with recurrent abdominal pain.

The diagnostic procedure of choice is technetium Tc 99m pertechnetate scanning.

Juvenile polyps may occur in as many as 1% of children, with peak incidence from 2 to 5 years of age. The common clinical presentation is recurrent, painless bleeding with a small amount of blood on formed stool. Diarrhea and tenesmus can occur when the polyp is large and located in the left colon.

Typical juvenile polyps are smooth, rounded, and red. Polyps of less than 1 cm are usually sessile; polyps larger than 1 cm have short or long stalks. Juvenile polyps are composed of normal but cystically dilated crypts embedded in an abundant lamina propria. Colonic mucosa adjacent to the large polyp has a distinguished, so-called chicken skin appearance. Colonoscopy is indicated due to the high incidence (almost 50%) of coexisting of the rectal polyps with polyps in the more proximal portions of the colon.

Endoscopic polypectomy is the treatment of choice. There is a general consensus that a single juvenile polyp is not a premalignant condition. Therefore, removal of a solid juvenile polyp is curative. Surveillance colonoscopy is not indicated unless the child develops a new episode of rectal bleeding or retains 5 or more juvenile polyps.

Hemolytic uremic syndrome (HUS) should always be suspected in infants and toddlers with bloody diarrhea, which is present in three-quarters of children with epidemic HUS. In two-thirds of these children, *Escherichia coli* O157:H7 can be isolated. Bloody diarrhea in HUS results from hemorrhagic colitis caused by the presence of endothelial damage produced by verotoxin and Shiga toxin and submucosal hemorrhages. Tenesmus is common. Diffuse, severe abdominal pain with peritoneal signs can occur.

The presence of the so-called thumbprinting sign on a contrast enema or a computed tomography scan reflects a submucosal hemorrhage of the colon. Colitis-related symptoms last no longer than a week, followed by signs of hemolytic anemia and oliguria. Known GI complications of HUS are intussusception, pancreatitis, and intestinal obstruction. Small or large bowel perforation may occur during peritoneal dialysis, which may be performed to manage the acute renal failure that can accompany HUS.

Henoch-Schönlein purpura is most common in children younger than 7 years; the median age of appearance is 4 years. It should be suspected in children with sudden onset of severe diffuse abdominal pain, vomiting, and hematochezia following a viral illness during the winter and early spring and about a week after the appearance of purpuric-type skin lesions on the buttocks or lower extremities.

On rare occasions, GI manifestations may precede the skin rash. Severe anemia is uncommon. The small and large bowels have different degrees of hemorrhagic lesions. These may be apparent on a small bowel radiograph series or contrast enema with coarsening of folds and thumbprinting. Abdominal pain and hematochezia are self-limited. Treatment with corticosteroids is controversial, although it may shorten the course of GI symptoms of abdominal pain by 1 or 2 days.

Children 7 Years and Older

The common causes of GI bleeding in this age group are listed in Table 122.2.

Drug-induced gastritis or *acute ulcer* should be strongly suspected in children treated with NSAIDs or oral steroids. The degree of bleeding ranges from mild to moderate. The typical clinical presentation is the sudden onset of abdominal discomfort followed by hematemesis or melena. Two types of lesions can occur: gastropathy or acute gastric ulcers due to alteration of the mucosal microcirculation, and mucosal cytoprotection related to suppression of local synthesis of prostaglandins. The incidence of NSAID-related GI bleeding is much higher in patients with *Helicobacter pylori* gastritis. Therefore, eradication of *H pylori* infection is recommended before long-term therapy with NSAIDs.

Although peptic ulcer disease is relatively rare in pediatric patients, it accounts for at least one-third of the cases of upper GI bleeding in school-age children. Most bleeding ulcers are located in the duodenal bulb. At least 80% of bleeding episodes from duodenal ulcers cease spontaneously. However, if the bleeding is arterial, it may become life-threatening. Urgent endoscopy is necessary as soon as the patient becomes more stable after fluid resuscitation.

Risk factors for recurrent bleeding are large ulcer (>2 cm), location of the ulcer on the posteroinferior wall of the duodenal bulb, blood spurting from the base of the ulcer, a visible vessel, or an adherent clot. In these circumstances, the risk of recurrent bleeding is relatively high even after initially successful endoscopic hemostasis and acid suppression with intravenous (IV) infusion of proton pump inhibitors. The most critical time for rebleeding is the first 3 days following the initial hemostasis.

The risk of recurrent bleeding is minimal in children with a clear base ulcer or a pigmented spot sign, a small flat thrombus in the center of an ulcer. Endoscopic hemostasis is not indicated in these cases. Hemodynamically stable children without the endoscopically identified risk factors can be treated safely on an outpatient basis.

Colitis is the most common cause of rectal bleeding in older children and teenagers. Infectious colitis is by far more common than inflammatory bowel disease. In general, *bacterial colitis* is an acute, self-limited disorder manifested by sudden onset of fever, tenesmus, and bloody diarrhea lasting from 5 to 7 days.

Diarrhea lasting 4 weeks or longer is usually associated with chronic inflammatory bowel disease. Rare causes of chronic infectious colitis are *Yersinia enterocolitica,* tuberculosis, *Entamoeba histolytica, Strongyloides stercoralis,* and opportunistic infections in immunocompromised patients.

Clostridium difficile colitis should be ruled out, especially in children treated with antibiotics or hospitalized patients.

Ulcerative colitis usually presents with insidious onset of diarrhea, nocturnal diarrhea, and subsequent hematochezia. Clinical manifestations of moderate to severe forms of ulcerative colitis include bloody diarrhea, abdominal cramps, urgency to defecate, malaise, anorexia with weight loss, intermittent low-grade fever, and some degree of anemia and hypoalbuminemia.

Crohn disease has a more indolent onset associated with abdominal pain, diarrhea, poor appetite, and weight loss. Diarrhea is not grossly bloody unless there is bleeding from an anal fistula or colitis that is diffuse or left sided.

Differentiation between bacterial colitis and the early stage of chronic inflammatory bowel disease is always a challenge. A high index of suspicion and negative bacterial stool culture results, including *Yersinia* species and other rare pathogens, are essential parts of early diagnosis. The definitive diagnosis of chronic inflammatory bowel disease is based on the results of upper and lower GI endoscopy, including multiple biopsies.

Management

Resuscitation

It is imperative to initiate resuscitation of the patient who is hemodynamically unstable almost immediately before any diagnostic procedure is considered. Two large-bore peripheral IV catheters or a central catheter should be placed and secured. Blood is typed and crossmatched and sent for baseline laboratory assessment of levels of hemoglobin, hematocrit, MCV, platelets, electrolytes, creatinine, blood urea nitrogen, liver enzymes, and clotting factors. Oxygen

supplementation and large boluses of saline target restoration of circulation and tissue oxygenation. The volume of isotonic solution should be sufficient to improve tachycardia and reverse narrow pulse pressure. Blood transfusion is indicated for patients with

- Persistent tachycardia, abnormal pulse pressure, or orthostatic hypotension after replacement of 15% to 20% of blood volume with isotonic solution.
- Estimated blood loss of 30% or more.
- Hemoglobin of 6 g/dL or less.
- Uncontrolled bleeding.
- Hemorrhagic shock.
- Hemoglobin of 7 to 9 g/dL in children with chronic heart and lung diseases and signs of hypoxia.

Packed red blood cells are the product of choice for replacement of blood loss. Matched whole blood is preferred for patients with massive bleeding. Fresh-frozen plasma is indicated for children with suspected or documented clotting factor deficiency, including those with acute or chronic liver disease. Platelet transfusion is indicated in rare cases of severe bleeding with estimated blood loss of more than 50% of the patient's blood volume or children with active hemorrhage and platelet count less than 50,000 platelets/mm^3. Early blood transfusion is reasonable for children with active bleeding and known chronic heart or lung diseases. Monitoring of vital signs is a more accurate means of assessing the effect of blood transfusion than monitoring of hematocrit soon after transfusion. It is reasonable to wait 6 hours before checking a posttransfusion hematocrit.

Octreotide (a synthetic somatostatin analogue) is an effective adjuvant medical therapy of severe bleeding from esophageal or gastric varices. It should be given to the child with active hemorrhage and any evidence of chronic liver disease or previously diagnosed portal hypertension. The initial IV bolus of 1 mcg/kg is followed by continuous infusion of octreotide with the initial rate of infusion as 1 mcg/kg per hour. The dose can be increased every 6 hours up to 5 mcg/kg per hour.

Endoscopic hemostasis is a standard therapy for moderate to severe upper GI bleeding related to peptic ulcer disease, esophageal or gastric varices, and vascular malformation.

Surgery should be reserved for children with severe uncontrolled bleeding from a known source or specific disorders, such as Meckel diverticulum.

Prognosis

The prognosis for infants and children with GI bleeding depends on the condition causing the bleeding. Early, aggressive treatment of the consequences of blood loss is essential to decreasing morbidity and mortality. Generally, prognosis is good, and overall mortality is less than 5%.

CASE RESOLUTION

The young child with hematemesis and splenomegaly had esophageal bleeding secondary to extrahepatic portal hypertension. The diagnosis was established during upper GI endoscopy and a negative workup for liver disease. The bleeding was controlled with a banding procedure. Long-term follow-up is indicated for proper management of this patient's condition and timely referral for surgery, if indicated.

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CHAPTER 123

Diarrhea

George Gershman, MD

CASE STUDY

An 11-month-old boy is evaluated for poor weight gain, decreased appetite, and diarrhea for the past 3 months. The parents report 3 to 4 bowel movements a day. They describe stool as "mushy" and "foul smelling." There are no ill contacts and there is no history of recent travel. The vital signs are normal. The patient appears pale and malnourished with wasted buttocks. His weight is at less than the 5th percentile, and his length is at the 25th percentile. The mucous membranes are moist without ulcers. The abdomen is soft and distended. Bowel sounds are active. There is no hepatosplenomegaly. Extremities are warm and well perfused.

Questions

1. What are the major categories of diarrhea?
2. What are the common infectious agents that cause diarrhea in infants and children?
3. What are the manifestations of acute and chronic diarrhea?
4. What conditions lead to persistent diarrhea in infants and children?
5. How is diarrhea managed in infants and children?

The word "diarrhea" is derived from Greek and means "to flow through." Diarrhea is associated with increased volume of stool caused by loose consistency and increased frequency of bowel movements. However, frequency of bowel movement and consistency of stool varies significantly from person to person and according to type of diet. For example, some healthy breastfed infants have a bowel movement once a week, whereas others may pass stool 7 to 10 times a day. The stool of breastfed infants is usually looser than that of formula-fed infants.

Diarrhea is a manifestation of various disorders, such as acute and chronic infections, chronic inflammatory bowel disease, food allergy or sensitivity, enzymes deficiency, hormonal imbalance, adverse effects of medications, mucosal atrophy, and short bowel syndrome, that affect either absorption of nutrients and water from the small and large intestines or secretion of fluids toward the intestinal lumen.

Epidemiology

Diarrhea is extremely common worldwide. In the United States, acute gastroenteritis is second in frequency only to upper respiratory tract infections. According to the World Health Organization, 2.5 million children in Latin America, Asia, and Africa die annually of dehydration secondary to diarrhea. In contrast, approximately 400 children die of this condition in the United States each year. These children often come from families of lower socioeconomic status.

In the United States, each child experiences an average of 0.9 episodes of diarrhea per year unless enrolled in a child care facility. In that case, the number increases to up to 3.2 episodes per year, a figure similar to that experienced by children in developing countries. In developing countries, the reported episodes of acute diarrhea vary from 3 to 6 to 8 in certain areas per year in children younger than 5 years. The severity of the infection is influenced by the underlying state of nutrition. An episode of acute gastroenteritis can be devastating for a child who has malnourishment. The fecal-oral route is the major path for the spread of infectious diarrhea. In developing countries, poor sanitation and contaminated drinking water perpetuate the problem. In the past 2 decades, the childhood mortality rate associated with diarrhea declined slowly but steadily primarily because of improved access to oral rehydration solution.

Many pathogens can be responsible for infectious diarrhea. The prevalence of individual pathogens varies widely between geographic areas and among different age groups. For instance, bacterial infections are more common in the first few months after birth and then again in school-age children. Rotavirus, the single most ubiquitous cause of infectious diarrhea worldwide, peaks between 6 and 24 months of age. In recent years, because of the widespread use of rotavirus vaccine in US children, norovirus has become the leading cause of medically attended acute gastroenteritis in the United States and is not only responsible for at least 50% of all outbreaks but the major cause of foodborne illness. On the contrary, *Escherichia coli* occurs frequently as a sporadic bacterial cause of diarrhea in the United States.

Definitions

Diarrhea is defined as stool mass more than 10 g/kg in infants and more than 200 g in older children. In clinical practice, and in accordance to the World Health Organization, it is acceptable to define diarrhea as "the passage of 3 or more loose or liquid stools per day, or more frequently than is normal for the individual."

Acute diarrhea is characterized by sudden onset and resolution of diarrhea within 2 weeks. *Persistent diarrhea* implies an acute onset of diarrhea that lasts at least 14 but less than 30 days. The definition is based on acute-onset diarrhea that continues beyond the expected duration of an infectious etiology. *Chronic diarrhea* is defined as diarrhea lasting 30 days or more and associated with specific causes (eg, celiac disease, inflammatory bowel disease).

Clinical Presentation

The manifesting symptoms of diarrhea include frequent, watery stools, which may contain blood or mucus. Affected children may experience fever, vomiting, bloating, and abdominal pain. Signs and symptoms of dehydration such as decreased skin turgor, dry mucous membranes, depressed fontanelle, diminished tearing, and tachycardia may be present. Persistent diarrhea may be associated with weight loss and inability to gain weight at an appropriate rate (Box 123.1).

Pathophysiology

Regardless of etiology, diarrhea by definition results from an imbalance in intestinal handling of water and electrolytes. Water transport through the wall of the intestine is always a passive process linked to the active absorption of sodium and chloride. Regulatory mechanisms of water and electrolyte transport across the intestine require integration of the enteric nervous system, cells in the lamina propria mucosae, and epithelial cells. This complex system works through the generation of hormone peptides, active amines, arachidonic acid metabolites, and nitric oxide. The bulk of absorbed water crosses the intestinal epithelium between the cells (tight junctions) following generation of the osmotic gradient by the transport of nutrients and electrolytes. The normal flow of water across the intestine can be disrupted, leading to diarrhea, by 2 processes: (1) excessive osmolality within the intestine caused by either consumption of large amounts of nonabsorbable sugars, such as lactulose, or maldigestion or malabsorption of 1 or more nutrients (eg, monosaccharides or disaccharides) and (2) active secretion of water by enterocytes affected by viral or bacterial infection, toxins, and other substances.

Box 123.1. Signs and Symptoms Used in the Diagnosis of Persistent Diarrhea

- Liquid stools
- Frequent stools
- Blood in stool
- Mucus in stool
- Fever
- Poor weight gain, or weight loss
- Dehydration
- Vomiting
- Abdominal pain

Osmotic diarrhea occurs whenever digestion or absorption is impaired. In general, it is relatively small-volume diarrhea, which is dependent on oral intake and abolished with fasting. The most common causes of osmotic diarrhea are

1. Malabsorption of carbohydrates caused by either excessive consumption (eg, concentrated formulas or carbonated beverages) or decreased production of brush-border enzymes or the presence of nonabsorbable substances such as lactulose, sorbitol, or magnesium salts in the intestinal lumen.
2. Decreased absorptive capacity of the intestine caused by acute or chronic inflammation of the small-bowel mucosa (eg, acute viral gastroenteritis, cow's milk protein allergy, bacterial overgrowth, giardiasis, celiac disease).
3. Lack of pancreatic enzymes or bile acid.
4. Decreased absorptive capacity of the small intestine secondary to congenital or acquired short bowel syndrome. Recent data suggest that improper differentiation of intestinal enteroendocrine cells has profound effects on the nutrient absorption by the small intestine.

In general, unabsorbed nutrients create an osmotic load that stimulates water leakage into the intestinal lumen across the tight junction. In addition, unabsorbed nutrients, such as carbohydrates, are the substrate for fermentation by colonic bacteria with liberation of short-chain organic acids, which create a secondary osmotic load in the large intestine and exacerbation of osmotic diarrhea.

Secretory diarrhea can be induced by any process, which creates a state of active intestinal secretion. In general, *secretory diarrhea* is associated with intestinal loss of large volumes of fluids, which continues despite cessation of eating. In the case of isolated small-bowel involvement, the large intestine will partially compensate losses of water and electrolytes. The most common cause of secretory diarrhea is bacterial infection. The other triggers of secretary diarrhea could be viruses (eg, rotavirus, HIV) or protozoan enterotoxins (eg, *Cryptosporidium parvum* in compromised immune systems). Secretory diarrhea is also seen in patients with neuroendocrine tumors, such as carcinoid tumors, gastrinomas, ganglioneuroblastomas, and congenital disorders of fluid and electrolyte metabolism, such as congenital chloridorrhea. The classic example of secretary diarrhea is infection with enterotoxigenic *E coli,* and *Vibrio cholerae.* Both bacteria produce toxins that bind to specific enterocyte membrane receptors and activate adenyl cyclase and production of cyclic adenosine monophosphate (by cholera toxin and heat-labile toxin from enterotoxigenic *E coli*) or cyclic guanosine monophosphate (by heat-stable toxin produced by *E coli*). The ultimate pathway involves the opening of chloride channels and massive water loss. Secretory diarrhea is particularly common in the developing countries, where it is related to infection with organisms such as enterotoxigenic *E coli,* and *V cholerae.* In the United States, the most common cause of secretory diarrhea is rotavirus infection. Vasoactive intestinal peptide-secreting tumors such as ganglioneuroma and neuroblastoma must be considered in children with persistent secretory diarrhea.

Both osmotic components and secretory components are present in many cases of diarrhea.

Motility disorders such as pseudo-obstruction syndrome or colonic inertia can be associated with persistent nonspecific diarrhea.

Inflammatory diarrhea can be acute, self-limiting (caused by intestinal infections) or chronic (eg, caused by inflammatory bowel disease or a few bacterial pathogens, such as *Yersinia enterocolitica,* or tuberculosis).

Steatorrhea is defined as presence of excessive amount of fat in the stools. Normally, at least 95% of fat is absorbed. In infants younger than 12 months, 10% of ingested fat may appear in the stool. Steatorrhea can result from fat malabsorption in children with mucosal atrophy (eg, celiac disease) or maldigestion secondary to chronic liver and pancreatic disorders (eg, biliary atresia, cystic fibrosis). Steatorrhea may also be seen in patients who have giardiasis.

Differential Diagnosis

Acute Diarrhea

The major cause of diarrhea in children and infants is acute viral gastroenteritis. The most common virus causing it is rotavirus, which usually spreads during the winter months, hence the term "winter vomiting disease." Infants present with a history of antecedent mild upper respiratory tract symptoms, followed by fever and vomiting. Watery diarrhea, which is usually free of blood or mucus, then occurs. About 10% of children who have rotavirus infection have signs of otitis media. Dehydration may also occur. Patients typically exhibit mild hypernatremia, with serum sodium values reaching 150 mEq/L. The incidence of rotavirus infection is markedly reduced following the universal administration of rotavirus vaccine. Enteric adenovirus infection is the second most common cause of acute diarrhea.

The most common bacterial agents associated with gastroenteritis in the United States are *Shigella, Salmonella,* and *Campylobacter. Aeromonas,* a common pathogen in developing countries, is recovered in less than 1% of cases of diarrhea in the United States.

Campylobacter produces signs of colitis, with blood and mucus in the stools. Patients are usually febrile and experience abdominal cramps. As a rule, children infected with *Shigella* have more systemic symptoms (eg, higher grade fever, marked leukocytosis). In addition, infants and toddlers are particularly prone to seizures. Tenesmus and blood in stool are common. Infection with *Salmonella* may also be associated with high fever. Stools may be watery or mushy and often contain a large amount of mucus. Parasitic infections, particularly with *Giardia lamblia, Entamoeba histolytica,* and *C parvum,* may be associated with diarrhea and may follow a more protracted course. Infestation with these organisms does not usually result in fever.

Otitis media and urinary tract infection may also be accompanied by diarrhea. Sixty percent of children with hepatitis A develop diarrhea in the first week of illness. Other conditions may also result in diarrhea. In newborns, infection with *E coli* may produce epidemic outbreaks of large, explosive green stools without blood. Such outbreaks could result in closure of newborn nurseries. Changes in stool consistency in conjunction with feeding intolerance and abdominal distention could be related to necrotizing enterocolitis, especially in preterm infants. Although the exact etiology of necrotizing enterocolitis remains unknown, it is believed that intestinal immaturity leads to a compromised intestinal epithelial barrier, an underdeveloped immune defense, and altered vascular development and tone. The compromised epithelial barrier and underdeveloped immune system, when exposed to luminal microbiota that have been shaped by formula feedings, antibiotic exposure, and cesarean section, can lead to intestinal inflammation and sepsis. Feeding intolerance, bloody stools, pneumatosis intestinalis, and air in the portal vein are the hallmarks of the disorder. Enterocolitis may also occur in infants with Hirschsprung disease (ie, congenital megacolon). Adrenal insufficiency, as well as certain inborn errors of metabolism (eg, galactosemia), may lead to diarrhea. In general, other symptoms such as vomiting occur. Infants may present in shock because of hypovolemia related to dehydration.

Food intolerance may result in diarrhea in infants as well as in older children. Overfeeding or the ingestion of large quantities of fruit juices, dried fruits, or sorbitol-containing products can produce osmotic diarrhea. Food allergies may also be associated with malabsorption. Infants with cow's milk protein allergy can experience diarrhea, growth impairment, anemia, hypoproteinemia, edema, respiratory symptoms, and eczema. Eosinophilia and elevated levels of immunoglobulin E are uncommon in infants with cow's milk protein allergy. High cross reactivity between cow's milk protein and soybean protein in up to 50% of children with cow's milk protein allergy explains a lack of clinical response after substitution for soy protein-based formula. However, soy-containing formulas are very effective in infants with lactase deficiency. Congenital lactose intolerance is an extremely rare disorder. Acquired lactase deficiency is fairly common, especially in certain racial groups; it is reported in 10% of white patients, 70% to 80% of black patients, and 90% of Asian patients. The disorder is associated with diarrhea, cramping, and bloating after consumption of lactose. The stool has an acid pH, floats because it contains air, and is positive for reducing substances. Lactase deficiency may occur following an episode of acute gastroenteritis, when the brush border of the small intestine has been disrupted.

Persistent Diarrhea

Infants and children may have a protracted course of loose stools following an episode of acute gastroenteritis. Risk factors for persistent diarrhea are caloric and protein malnutrition, vitamin A and zinc deficiency, prior infection (eg, measles), male biological sex and young age (6–24 months), and young maternal age.

In most cases, no cause for persistent diarrhea can be detected, but infestation with *Shigella* species or enterotoxigenic *E coli* may be a contributing factor. The possibility of infection with HIV should be considered in infants and children with protracted diarrhea, especially in geographic areas in which disease prevalence is high.

Certain children with acute diarrhea have such a modified diet (eg, clear fluids) that they develop starvation stools. These slimy, dark green or golden stools represent *succus entericus*, the secretion of the small intestine. Starvation stools do not have a fecal odor. Insufficient fat in the diet may contribute to starvation-associated diarrhea.

Chronic Diarrhea

Inflammatory bowel disease, which occurs more commonly in older children and adolescents, is associated with chronic diarrhea. Ulcerative colitis manifests with infiltration of the lamina propria mucosae with inflammatory cells, distortion of the glands, and crypt abscesses. Fever, weight loss, and anorexia are often present. Diarrhea is the hallmark of the disease, and patients experience tenesmus as well as mucus-laden and bloody stools. Inflammation always affects the rectum. It can be localized in the descending colon (left-side colitis) or spread out through the entire large intestine (pancolitis).

Crohn disease may also lead to chronic diarrhea, although lower abdominal pain aggravated by defecation may be a more prominent part of the medical history. Affected individuals frequently experience extraintestinal manifestations of the disease, such as fever, anorexia, weight loss or growth impairment, recurrent stomatitis, uveitis, arthralgia and arthritis, and clubbing. Perianal disease, such as fistulas, may be noted in 30% of patients.

Irritable bowel syndrome (IBS) may lead to chronic diarrhea in infants and children. Affected children do not experience diarrhea at night, which is the sign of infectious or secretory diarrhea. Partially formed or liquid-first stool in the morning and increased frequency during the day are characteristic of IBS. Bowel movement tends to occur after each meal, suggesting a prominent gastrocolic reflex. Children have 3 to 10 mucus-containing stools per day. Alternating periods of constipation may occur. Affected children appear well throughout this illness, without weight loss, growth impairment, fever, leukocytosis, steatorrhea, or protein malabsorption. Their appetite remains good. The first line of treatment of children with IBS-predominant diarrhea is a high-residue diet. Different probiotics have been used recently for treatment of IBS in children with various success rates.

Other frequent causes of chronic diarrhea are consumption of a large amount of fruit juice or carbonated beverages and adverse effects of medications such as antibiotics or nonsteroidal anti-inflammatory drugs.

Many rare conditions can lead to chronic diarrhea: autoimmune enteropathy, microvillus inclusion disease, and intestinal polyposis. Chronic diarrhea may also be associated with maldigestion, as with cystic fibrosis, or malabsorption, such as with celiac disease, or gluten sensitive enteropathy.

Newborns with cystic fibrosis may present with meconium ileus or, rarely, with acute appendicitis. Failure to thrive is common among patients with cystic fibrosis even though many of them have voracious appetites. Stools are large, bulky, and foul smelling secondary to the steatorrhea. Isolated gastrointestinal (GI) concerns are reported in 15% to 20% of patients with cystic fibrosis. Rectal prolapse is not uncommon. Most affected children also experience recurrent pneumonia and chronic pulmonary disease.

Celiac disease is an immune-mediated disorder related to gliadin, a portion of gluten, a protein found in wheat, barley, rye, and oat. Characteristically, a various degree of villous atrophy is apparent on tissue from a small intestinal biopsy. This flattening restricts the absorptive capacity of the intestine and leads to malabsorption. Children with the classic form of celiac disease have short stature, pale skin, sparse hair, protuberant abdomen, and wasted buttocks. In recent reports, subtle signs of celiac disease have been recognized and usually reflect the growth impairment, anemia, iron and folate deficiency, short stature, abnormal liver enzyme levels, dental enamel defects, osteoporosis, delayed puberty, and neurological abnormalities. Symptoms appear a few months after grains are introduced into the diet, usually between the ages of 9 and 12 months. Stools are mushy, bulky, and foul smelling. Fat content in the stool may be 2 to 3 times the normal level.

Evaluation

History

A comprehensive history derived from proper structured and targeted questions is the key for correct approach to the accurate diagnosis of diarrhea (Box 123.2).

Physical Examination

Children should be assessed for the presence of dehydration: altered vital signs, delayed capillary refill, decreased skin turgor, a sunken fontanel, dry mucous membranes, and reduced tearing. Detailed physical examination may reveal signs suggestive of specific diagnosis. For example, persistent severe skin changes in the perianal area or the perianal fistula should trigger a further workup to rule out acrodermatitis enteropathica and Crohn disease, respectfully. Evidence of growth impairment should be determined by assessing the growth parameters. Inability to gain

Box 123.2. What to Ask

Diarrhea

- How long has the diarrhea been present?
- How frequent are the bowel movements?
- What is the consistency of the stools?
- Is the diarrhea related to eating, which is a sign of osmotic diarrhea, or does it occur even if the child does not eat, which is a sign of secretory diarrhea?
- Do the stools contain any blood or mucus, which suggests a bacterial or parasitic infection?
- Is the child febrile?
- Does the child have any symptoms associated with the diarrhea?
- Does the child have a recent history of travel or exposure to animals?
- Is anyone at home ill?
- Has the child experienced any change in the frequency of urination, which is an important measure of the state of hydration?
- What is the child's diet now? What has it been?

weight over a period of months should initiate the workup of GI disorders such as chronic inflammatory bowel disease, celiac disease, or cystic fibrosis.

Laboratory Tests

The characterization of acute or chronic diarrhea begins with 4-step stool analysis. First, stool is evaluated for its quantity as well as its gross appearance. Undigested pieces of fruits and vegetables in stool of toddlers are often a sign of poor chewing. Small, threadlike bodies that resemble worms could be bile concretions common in infant stool. A fluctuation of stool volume with fasting is important: resolution of diarrhea with fasting is a sign of malabsorption and osmotic diarrhea. Second, stool is subjected to chemical and microscopic analyses to detect the presence of unabsorbed nutrients such as carbohydrates and fats. The presence of carbohydrates could be detected by adding reducing substance tablets (eg, Aim Tab Reducing Substance Tablets) to a small amount of stool liquefied in 1 mL of water. A change in color from blue to green or orange is indicative of undigested carbohydrate. If the main source of dietary sugar is sucrose, as determined by the history, the specimen must be hydrolyzed by heating with hydrochloric acid. The specimen should be analyzed quickly because the normal stool bacteria may break down the carbohydrate and lead to a false-negative result. The presence of fat can be determined both qualitatively and quantitatively. A microscopic examination of stool treated by Sudan or Carmine red stains highlights neutral fat inclusions. Presence of 10 or more globules of fat per high-power field indicates a 3-day stool collection for quantification of undigested fat. Fecal elastase test is a valid alternative to 3-day stool collection.

Third, stool is examined for the presence of blood and leukocytes. Blood may be present in stool but originate from excoriations in the diaper area rather than from the GI tract. A simple way to find stool leukocytes is to smear a mucous component of the stool onto a glass slide and stain it with methylene blue. More than 2 to 4 leukocytes per high-power field is abnormal and is suggestive of a bacterial infection. The sensitivity of the fecal leukocyte test is 85%, but the specificity is only 50% to 60%. Absence of leukocytes or erythrocytes in the stool signifies a very low probability of an invasive bacterial infection (predictive value of a negative test is 95%). A liquid stool should be submitted for culture of potential ova and parasites. Stool analysis using an antibody immunoassay test (eg, Rotazyme) will detect rotavirus.

Fecal calprotectin and lactoferrin tests are sensitive and specific tests to assess the activity of chronic intestinal inflammation.

Fourth, stool is assessed for levels of sodium and potassium and stool osmolarity to calculate the so-called ion gap (ion gap [mOsm/kg] = stool osmolarity [290 mOsm] – 2[(sodium [mEq/L] + potassium [mEq/L])]). Ion gap exceeding 100 mOsm/kg and low sodium concentration in stool (<40 mEq/L) is typical with osmotic diarrhea. On the contrary, ion gap equal to or lower than 100 mOsm/kg and sodium concentration in stool higher than 70 mEq/L is consistent with secretory diarrhea.

Additional studies, especially in the face of dehydration or fever, include serum electrolyte levels study, complete blood cell count, urinalysis, and urine culture. Upper GI endoscopy with a small bowel biopsy is indicated for diagnosis of such diseases as celiac disease or other causes of persistent or chronic malabsorptive diarrhea. Colonoscopy should be considered after consultation with a gastroenterologist if inflammatory bowel disease is suspected.

Management

Initial management of children with gastroenteritis involves adequate oral hydration and correction of electrolyte deficits (see Chapter 80). Intravenous fluid therapy may be necessary in children who cannot tolerate oral rehydration. Children with significant dehydration may require admission to the hospital. Less severely affected children could be managed as outpatients using glucose-based oral rehydrating solutions such as Pedialyte or Infalyte. Alternatively, parents can be advised to make oral rehydrating solutions by using water (1 L [4 c]), sugar (20–39 mL [4–8 tsp]), and salt (2½ mL [½ tsp]).

Dietary manipulation in the treatment of diarrhea is somewhat controversial. Traditionally, affected children have been placed onto clear fluids for 1 or 2 days, with a gradual return to a more regular diet with time. A BRAT diet (bananas, rice or rice cereal, applesauce, and tea or toast diet) was often recommended because of the intrinsic binding properties of the particular food. Authors of recently published studies recommend a full resumption of a normal diet, including dairy products, as the way to ensure adequate nutrition during the acute illness. A high-fat, low-carbohydrate diet accelerates improvement. A lactose-free diet is beneficial for infants and children with persistent diarrhea.

Antimicrobial therapy is indicated for infection with certain pathogens, such as *Campylobacter* species, *E histolytica, G lamblia,* and *Shigella* species. Antimicrobial agents are used to treat *Salmonella* species infection in certain populations, such as neonates, immunocompromised children, and children with sickle cell anemia. Antidiarrheal agents are not usually recommended for the management of diarrhea in children. Diarrhea is believed to be the body's way of eliminating a toxic substance that has been ingested.

Zinc supplementation has been found efficacious in preventing and treating acute diarrhea in developing countries. The World Health Organization and UNICEF (United Nations Children's Fund) recommend zinc supplementation of 10 mg as syrup for infants younger than 6 months and 20 mg for children as dispersible tablets per day for 10 to 14 days.

Probiotics such as of lactobacilli, *Bifidobacterium* species, and *Saccharomyces boulardii* may shorten the course of diarrhea or prevent complications associated with acute diarrhea.

The management of children with chronic diarrhea should target the underlying disorder.

Prognosis

Most cases of acute diarrhea in infants and children in the United States are self-limited and resolve without consequences. Chronic diarrhea may lead to malnutrition and other complications, such as growth impairment. Enteral feedings or hyperalimentation may be used to ensure adequate nutrition and a good outcome. Some children require consultation with a pediatric gastroenterologist.

CASE RESOLUTION

A constellation of chronic diarrhea, poor weight gain, decreased appetite, and foul-smelling stool is suggestive of steatorrhea as seen in patients with celiac disease. Laboratory tests for celiac disease can be requested by the primary care physician and consultation with a pediatric gastroenterologist considered.

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CHAPTER 124

Constipation

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CASE STUDY

A 9-year-old girl is brought to the office by her mother with a report of bloody stool. The mother states that the blood is bright red and seen on the toilet paper and dripping into the bowl but that no blood is mixed into the stool. The child reports perianal pain that is burning during defecation and says that the bleeding is noted toward the end of the bowel movement. On further history, the child has been complaining of intermittent, colicky abdominal pain. This occurs mostly in the afternoon and evening and is relieved with bowel movements. Passage of stool is reported to be infrequent, with multiple skipped days in between. The mother recalls that the toilet has been plugged a few times after her daughter used it. The child has not experienced weight loss and eats an age-appropriate diet that is high in pasta, cheese, processed meat, breads, and candy. At times the child is gassy and looks bloated, but she is otherwise healthy, exhibiting normal growth and development. On examination, vital signs are normal. The patient is at the 65th percentile for height and the 80th percentile for weight. The abdomen is soft and nontender but mildly full in the left lower quadrant. Perianal examination reveals a deep anal fissure, and rectal examination reveals a firm fecal mass. The remainder of the examination is normal.

Questions

1. What is the definition of constipation?
2. How is the stooling pattern related to diet?
3. What conditions are associated with constipation?
4. How do familial factors influence stooling patterns?
5. What is the management of chronic constipation?

Constipation is a common and significant complaint that accounts for approximately 3% of visits to pediatric clinics and up to 25% of pediatric gastroenterology visits. Constipation is often associated with fecal incontinence and abdominal pain, can cause significant distress to the child and family, and has a significant effect on health care costs. Stools that are dry, hard, and difficult to pass define constipation. Although reduced stool frequency is a common characteristic of constipation, it is not universal. The guidelines of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition define constipation as "a delay or difficulty in defecation, present for two or more weeks and sufficient to cause significant distress to the patient." This definition is less stringent that the Rome III criteria, which classifies constipation into 2 groups based on patient age, with children younger than 4 years needing to meet 2 criteria for at least 1 month and those older than 4 years for at least 2 months. The 6 Rome III criteria are defecation frequency 2 times or fewer per week, fecal incontinence, retentive posturing, pain during defecation, large-diameter stools, and palpable rectal fecal mass. The average stool frequency is 3 to 4 per day during the first weeks after birth, which decreases to 1 to 2 per day with introduction of table foods by 1 year of age. After age 4 years and into adulthood, normal stool frequency can range from 3 per day to 3 per week.

Many factors influence the stool frequency in normal newborns, infants, and young children, including diet, familial pattern of intestinal motility, personal sensitivity, hygiene habits, hydration status, variable stressors, and intake of medications. Newborns and infants who are fed mother's milk exclusively may have long intervals—sometimes several days—between normal bowel movements, usually starting in the third month after birth, although the stool will remain loose and seedy. Introduction of solids starting at 6 months of age is often associated with additional slowdown in bowel frequency, and functional constipation may initiate as early as this time.

Functional constipation is constipation in the absence of organic disease; however, it is important to note that chronic constipation is also a condition that begets disease and, thus, must be managed appropriately. Constipation is 1 of several unique medical conditions that create a positive feedback loop—stool withholding results in worsening constipation as stretch receptors accommodate a distended rectum and contractile forces fail to result in a complete evacuation.

In infancy, peristaltic motility may be weak or poorly coordinated, and the lack of physical mobility or ambulation requires the infant to exert a physiologic effort (ie, Valsalva maneuver) to allow passage of stool. Parents or guardians may interpret "straining" as a sign of constipation despite the passage of soft, normal stools. Therapy in such cases, if necessary, is usually nonmedical and involves manual stimulation of the anal sphincters and bringing of the knees toward the chest in a "bicycle kick." Older infants and toddlers may have constipation secondary to food intolerance, such as cow's milk protein allergy, and removal of the inciting agent may result in complete resolution. Toilet training can prove to be a challenge, especially in toddlers with constipation, and stressful parent/guardian-child interactions may result in resistance to toilet training on the part of the child.

Commonly, chronic constipation in childhood is triggered by a painful evacuation that results in an unpleasant experience. School-age children may elect to withhold stool because of fear of toileting outside the home or because of social stressors (eg, parental divorce, bullying). Assessment of the etiology of constipation requires a careful medical history to determine the age of onset, characteristic of the stool, and presence of contributing or confounding factors. Comorbidities, such as anal fissures or overflow encopresis, may manifest over time and usually signify a more chronic course.

Epidemiology

Functional constipation is a common problem in childhood, with an estimated prevalence of 3% worldwide. Prevalence of constipation in infants is lower, but it increases between the ages of 2 and 4 years. The onset often coincides with toilet training and dietary changes and is partially a product of increased colonic transit time. Prevalence of constipation in infants and toddlers is equal among males and females, but it becomes 3 times more frequent in boys than girls by age 5 years. Fecal soiling is a significant comorbidity and is reported in up to one-third of females and one-half of all males with severe, chronic constipation (see Chapter 56).

Clinical Presentation

Infants often present with infrequent passage of stool, with some parents or guardians reporting facial grimacing and grunting during defecation as well as apparent discomfort or fussiness with bowel movements, defined by Rome III as *infant dyschezia*. History of delayed passage of meconium or onset of symptoms before 1 month of age, recurrent vomiting, poor weight gain, or family history of congenital megacolon (ie, Hirschsprung disease) or cystic fibrosis indicate the need for further evaluation. Toddlers usually present with abdominal pain and report the passage of hard or large stools. School-age children may present with fecal soiling, which usually represents overflow incontinence. (Only 10%–15% of all cases of encopresis consist of non-fecal retention.) Parents and guardians describe a stool-withholding posture in which the legs are clamped together and the gluteal muscles are contracted in an effort to suppress defecation (Figure 124.1). Poor appetite and episodic vomiting in severe cases are secondary to a persistent sense of fullness from a dilated and impacted colon. In infants, toxic megacolon resulting from Hirschsprung disease can present with lethargy and signs of sepsis, peritoneal signs, and bloody diarrhea. Hydronephrosis, urinary tract infections, and enuresis also are historically associated with chronic constipation and an impacted colon.

Physical examination should include growth parameters, abdominal examination, perianal inspection, digital rectal examination, inspection of the lumbosacral region, and neurologic evaluation for tone and deep tendon reflexes. The abdomen may be distended and contain a fecal mass on palpation; anal position must be confirmed, and the presence of stool present around the anus or on the undergarments, erythema, rash, skin tags, or fissures should be noted. Lumbosacral dimple, hair tuft, gluteal cleft deviation, and sacral agenesis must be excluded.

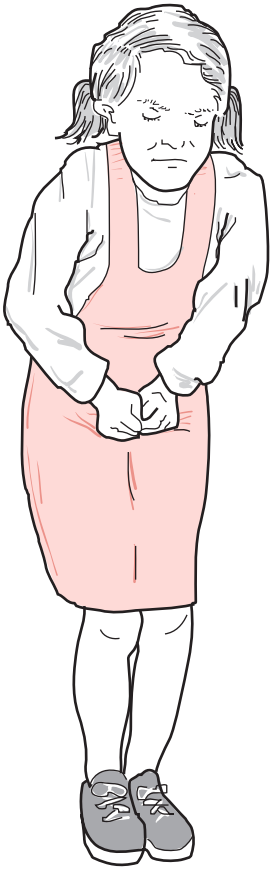

Figure 124.1. Child exhibiting retentive posture.

Pathophysiology

The Colon

The colon is a muscular organ that processes dietary residue through bacterial fermentation, salvaging nutrients and reabsorbing more than 90% of the water that enters, and prepares stool for transient storage and eventual excretion (Figure 124.2). Fermented food residue produces gas (eg, hydrogen, methane) and short-chain fatty acids; the latter provide colonocytes with readily available fuel (via butyric acid) that enters the portal circulation for calorie salvage in the liver (eg, propionic acid, acetic acid). The fermentation process may release other micronutrients and vitamins (eg, vitamins K_2 and B_{12}, folic acid, biotin) and is thus an important component of colonic function.

Normal Physiology

Digested food normally takes approximately 2 to 6 hours to reach the cecum from the duodenum (following gastric emptying, which has a normal half-time of 60–90 minutes). The propagation of food in the small intestine occurs via peristaltic waves called the *migrating motor complex.* Once chyme is in the cecum, peristalsis slows, and it may take several hours or days for it to be expelled as stool. The longer the transit time, the more extensive the water resorption and the more likely it is for the stool to be dry and hard. The rectosigmoid is the sensing organ that initiates the process of defecation and

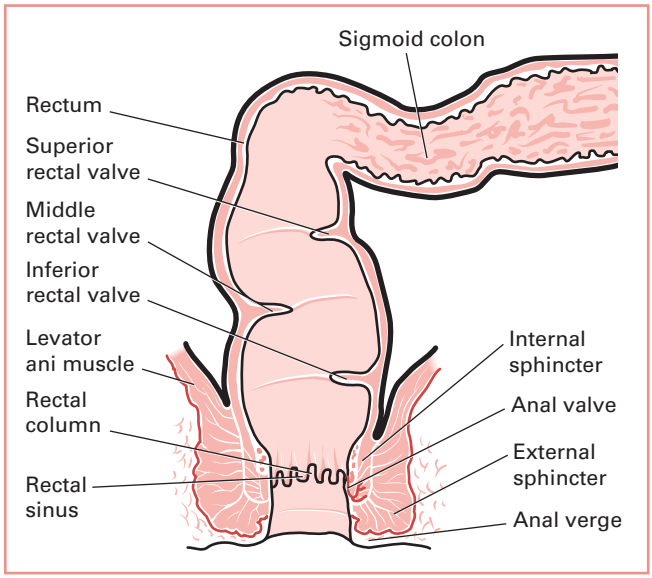

Figure 124.2. Diagram of the anus, rectum, and sigmoid colon.

can store stool until it is socially acceptable to expel it. Contraction and emptying of the rectosigmoid is stimulated by eating, a process called the *gastrocolic reflex.* In the rectum, the pelvic floor muscles (ie, levator ani, puborectalis muscle) regulate fecal retention and defecation. The puborectalis muscle suspends the rectosigmoid and imposes constraints that facilitate voluntary stool retention (ie, continence). Continence is also promoted by contraction of the internal and external anal sphincters.

Defecation

The urge to defecate is signaled by the propulsion of feces from the sigmoid colon to the rectum. Distention of the rectum causes relaxation of the internal anal sphincter; the external anal sphincter and puborectalis muscle must voluntarily relax through parasympathetic action. The pelvic floor muscles descend, permitting straightening of the anus and rectum (Figure 124.2). Thus, defecation is facilitated by squatting or sitting and by increasing intra-abdominal pressure. The urge to defecate can be consciously repressed by voluntary contraction of the external anal sphincter and likely subconscious sympathetic reflex inhibition and contraction of the puborectalis muscle. The process of defecation is learned early in childhood and remains spontaneous throughout life. The spontaneity of this process may be lost for a variety of reasons, including secondary to trauma, pelvic floor dysfunction, pseudo-obstruction, and surgical resection.

The Vicious Cycle of Constipation

If the urge to defecate is suppressed, the rectosigmoid and eventually the entire colon become dilated and impacted, and defecation may become difficult. The increased caliber of the colonic lumen makes contractions weaker and less effective in propagating stool. Moreover, the child with constipation may become desensitized to rectal distention. Eventually, delayed defecation results in the formation of hard, bulky stool, which makes defecation difficult and painful. The child learns to tighten the external anal sphincter and gluteal muscles, pushing feces higher into the rectal vault and suppressing the urge to defecate; this is the vicious cycle of constipation (Figure 124.3). In children, the initiating event may be a painful evacuation, possibly after an acute illness (eg, cold, respiratory infection) or a course of antibiotics. Intentional and prolonged suppression of defecation is an important factor in the pathogenesis of chronic constipation.

Familial Factors

Some families are predisposed to constipation. Concordance for constipation is 4 times more common in monozygotic twins than dizygotic twins. It may be related to increased absorption of water or an unusually long or poorly motile colon. Poor sensitivity to a critical rectal volume or the need for a particularly large rectal volume may delay the initiation of defecation in genetically predisposed individuals.

Differential Diagnosis

The differential diagnosis of constipation can be divided into congenital versus acquired and then into the following etiologic categories: anatomic; neurologic; hormonal; infectious/toxic; drug-induced/metabolic; functional; and other, such as genetic or allergic (Box 124.1). Functional constipation is often supported by a history that includes poor dietary and hydration habits, stool-withholding behavior, and a normal physical examination. Dietary history may reveal high consumption of cow's milk (>24 oz/day), cheese, or sugary fruit juice, as well as poor intake of fruits, vegetables, and whole grains. Stool withholding most commonly occurs in young, school-age children and often is a product of a stressful environment, such as a new sibling, a move, parental struggles, or a new school environment.

Chronic constipation that is resistant to medical therapy should not be ignored. Conditions such as congenital megacolon and congenital intestinal malrotation can present past the neonatal period and may result in intestinal devastation (eg, volvulus, ischemia). Several conditions are particularly important to consider when evaluating

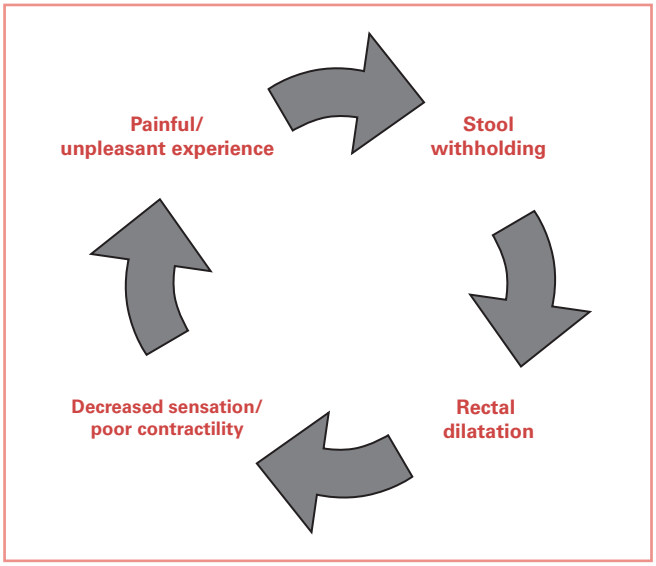

Figure 124.3. The vicious cycle of constipation.

Box 124.1. Differential Diagnosis of Constipation

Anatomic
- Anal stenosis
- Imperforate anus
- Ectopic anus
- Postoperative stricture

Neurologic
- Congenital megacolon (ie, Hirschsprung disease)
- Cerebral palsy
- Hypotonia
- Spina bifida occulta
- Meningomyelocele
- Sacral agenesis
- Intestinal pseudo-obstruction syndrome

Hormonal
- Hypothyroidism
- Panhypopituitarism
- Multiple endocrine neoplasia
- Pheochromocytoma

Infectious/Toxic
- Postinfectious ileus
- Botulism

Drug-induced/Metabolic
- Analgesic agents (eg, opioids)
- Antacids
- Anticholinergic agents
- Bismuth
- Iron
- Cholestyramine resin
- Hypocalcemia
- Hyperkalemia

Functional
- Dehydration
- Stool withholding
- Stress
- Anxiety
- Fear of painful evacuation

Other
- Cystic fibrosis
- Celiac disease
- Cow's milk protein allergy or sensitivity

constipation in infants, including congenital megacolon, hypothyroidism, anal stenosis or atresia, meningomyelocele, and cerebral palsy. Failure to pass meconium or a delay in the passage of meconium beyond 24 hours should raise suspicion for a congenital or genetic aberration (eg, congenital megacolon, cystic fibrosis).

Congenital megacolon is an intestinal motility disorder resulting from aganglionosis of the myenteric plexus that affects the rectosigmoid. In rare instances the entire colon is involved, although in most cases the distribution is distal to proximal. The severity of the disease and complexity of surgical treatment is directly proportional to the length of the affected colon. When ganglion cells are missing in the very distal portion of the rectum, the disorder may resemble chronic idiopathic constipation, which often may also be recalcitrant to medical therapy. The prevalence of congenital megacolon is approximately 1 in 5,000 live births and may account for up to 3% of all cases of constipation referred to a gastroenterologist. Physical examination of a patient with congenital megacolon may reveal some degree of abdominal distention and an empty rectal vault. In infants, a rectal examination frequently induces a gush of air and an explosive stool resulting from digital bypass of the diseased lumen. Early recognition of this condition is important to prevent the development of toxic megacolon and enterocolitis, a condition that carries high morbidity and significant mortality. Congenital megacolon may occur in conjunction with syndromes such as Down syndrome (ie, trisomy 21), Smith-Lemli-Opitz syndrome, and Waardenburg syndrome, and several genetic mutations in the receptor tyrosine kinase gene *RET* have been described as responsible for the pathogenic mechanism.

Infants with hypothyroidism secondary to hypopituitarism may also present with constipation and are not diagnosed through the newborn screening process because of normal (ie, low) levels of thyroid-stimulating hormone. These children may appear clinically normal or may display some of the features of hypothyroidism (eg, large fontanel, umbilical hernia, coarse facies, macroglossia).

Anal stenosis, imperforate anus with a perineal fistula, or an anteriorly displaced anus may not be recognized immediately in the newborn period because the condition may be quite subtle. Anorectal malformations occur in approximately 1 in 7,000 live births, which reinforces the need for a perianal and rectal examination with every constipated child.

Severe constipation that begins prior to toilet training is suggestive of an organic etiology, such as congenital megacolon, malrotation, or pseudo-obstruction. Pseudo-obstruction may present in the older child with a history of intermittent constipation, abdominal distention, pain, nausea, and vomiting. Onset of constipation around the time of toilet training, when stool consistency and pattern had been normal in the past, is suggestive of functional constipation.

In some children, constipation may develop in association with the use of medications such as iron or bismuth subsalicylate (eg, Pepto-Bismol), codeine or other narcotics, chemotherapeutic agents (eg, vincristine sulfate), and agents with anticholinergic properties (eg, pseudoephedrine, imipramine).

Evaluation

History

Commonly associated historical signs and symptoms of constipation include abdominal pain (especially during and after meals), abdominal distention, excessive flatulence, hard stools, dyschezia (ie, painful evacuations), bright-red blood per rectum, toilet plugging, and urinary symptoms (eg, enuresis, recurrent infections) (Box 124.2). Overflow incontinence may mislead the clinician to a differential diagnosis of chronic diarrhea. Fecal soiling resulting from stool retention and overflow is noted in many children with severe, chronic constipation, although a complete physical examination in such a setting should reveal a stool mass in the lower left abdominal quadrant and an impacted colon or rectum on digital manipulation. As with all conditions that present with abdominal pain, it is important to screen for the presence of recurrent mouth sores, skin rashes, joint pain, weight loss, bloody or mucous stools, incomplete evacuations, and tenesmus, which in the case of constipation consists of rectal spasm accompanied by a strong urge to defecate, often with the passing of blood or mucus. Family history of inflammatory bowel disease, celiac disease, irritable bowel syndrome, constipation, and atopy (eg, food allergy) should also be noted with every child presenting with abdominal pain.

Box 124.2. What to Ask

Constipation

- What is the child's stooling pattern? How often does the child have a bowel movement? What is the appearance and consistency of the stool?
- What was the child's age when the problem began?
- What makes up the child's diet?
- Does the child take any medications?
- Does the child have any symptoms associated with constipation, such as recurrent abdominal pain? If so, how long have these been occurring?
- Has the child been sick recently with any illnesses that might cause constipation?
- Has the child recently experienced any changes in routine that could cause constipation?
- Is there a family history of constipation?
- At what age was the child toilet trained?
- Is there any bleeding with passage of stool?
- Is there pain with passage of stool?
- Have any remedies, such as laxatives, enemas, or suppositories, been used to relieve the symptoms?

Physical Examination

The physical examination in individuals with functional constipation is usually normal. If the child reports abdominal pain, ask the child to indicate the area of greatest pain with 1 finger. In functional disease, the child most often points directly to the umbilicus. Palpation may reveal a firm stool mass in the left lower quadrant that is classically nontender. Consistency and color of the stool in the rectum varies, but a hard and dry stool is strongly suggestive of stool impaction. An empty rectum should raise suspicion for an organic etiology. Digital manipulation followed by an "explosive" passage of stool is suggestive of congenital megacolon (ie, Hirschsprung disease). The physician should examine the child's back for a sacral dimple or a hair tuft, especially in infants, which may be a sign of occult spinal cord anomaly.

Signs of pallor, mouth sores, hepatosplenomegaly, arthritis, or skin rashes may be suggestive of another underlying disease process.

Laboratory Tests

Malnourishment is possible if the child consumes a restricted diet (eg, >24 oz/day of cow's milk or soda) or has a suggestive physical examination (eg, pallor, dry skin). Iron deficiency anemia and mineral deficiencies (eg, calcium, zinc) are signs of poor nutritional intake. A lipid panel may reveal high triglyceride levels (from excessive sugar intake) and low high-density lipoprotein levels (from poor-quality fat intake). In some patients it may be necessary to evaluate thyroid function. Routine laboratory testing for hypothyroidism, celiac disease, and hypercalcemia is not recommended in children without suggestive symptoms.

Imaging Studies

Usually, a plain radiograph of the abdomen (ie, flat plate of the abdomen) is not indicated; however, it may help on a clinical level by showing the child and parents or guardians the significant amount of stool present. Anatomic studies, such as a barium enema to evaluate for malrotation, a congenital stricture, imperforate anus, or congenital megacolon, may be indicated if the history or physical examination is concerning. It is recommended for barium enema to be performed without a prior clean out to sensitize the study for the presence of a transitional zone. Evidence does not support the routine use of magnetic resonance imaging of the spine in patients with constipation without other neurologic abnormalities.

Additional Tests

Anorectal manometry and a suction rectal biopsy may be performed by a gastroenterologist to help diagnose congenital megacolon (ie, Hirschsprung disease); however, only a full-thickness rectal biopsy will confirm the presence or absence of aganglionosis, and this must be performed by a surgeon. Colonic manometry can also measure colonic peristaltic waves and help diagnose pseudo-obstruction and other dysmotility disorders. Evidence is conflicting for the role of allergy testing to diagnose cow's milk protein allergy or other food sensitivities.

Management

The Primary Care Setting

Most cases of constipation can be evaluated and managed by the primary care physician. In functional constipation, the mainstay of management involves a 3-pronged approach of dietary therapy, behavioral modification, and medications (Figure 124.4).

Diets that predispose to constipation are rich in simple carbohydrates (eg, sugar), refined and processed carbohydrates (eg, pasta), saturated fat (eg, fried food), processed meat (eg, hot dogs), and dairy (especially milk and cheese). Dietary therapy should begin by decreasing the intake of these food items and increasing the intake

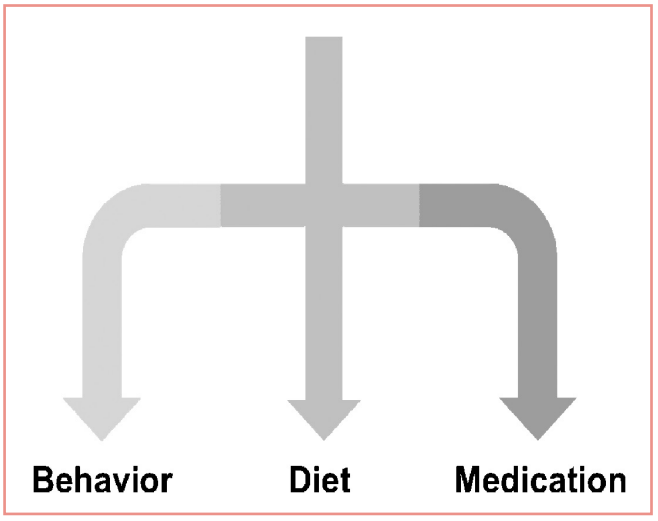

Figure 124.4. Three-pronged management of constipation.

of fruit, vegetables, whole grains, legumes, and tree nuts. Prune juice and fruit nectars (eg, pear, peach, apricot) may be supplemented, are well tolerated and effective, and may be mixed with the child's favorite drink. Most fruit, such as pears, papaya, and cantaloupe, as well as vegetables, roots, and tree nuts, are high in beneficial fiber. Dried fruits (eg, raisins, cranberries) are rich in sorbitol and thereby cathartic. It is important to continuously introduce new food items to the diet, especially fruit and vegetables. Introduction of certain foods, such as whole-grain breads and brown rice, may need to be gradual and may require some adjustment but will render lifelong benefits (Box 124.3).

Behavior modification can be challenging, but it is essential to breaking the vicious cycle. Teaching of proper toilet hygiene to the child should be done in a firm and consistent manner; engaging the child with a sticker or star chart may help. It is recommended that the child sit on the toilet once or twice daily for 8 to 10 minutes at a time, preferably after a meal, thereby taking advantage of the gastrocolic reflex. Longer toilet sitting should be discouraged, because it may result in perianal disease, such as a fissure or hemorrhoids. Even if the child does not have a bowel movement with each toilet sitting, good toilet hygiene will make the experience routine and, it is hoped, help prevent further reluctance to use the toilet. Biofeedback is useful when available, especially in the child with encopresis or paradoxical contraction of the external anal sphincter.

Medications are generally safe and mainly over-the-counter (Box 124.4). The 2 most commonly used medications are polyethylene glycol (PEG 3350), a nonabsorbable high–molecular weight synthetic polymer (nonfermentable), and lactulose, a nonabsorbable high–molecular weight sugar (fermentable). Both work by helping the colon retain water and thus prevent the complete dehydration of stool. Lactulose is a prebiotic that is fermented into short-chain fatty acid and can beneficially reduce stool pH. The process may cause gassiness and bloating in some patients, however, and therefore it may be necessary to gradually increase dosing. Suppositories or enemas and manual disimpaction should be avoided, because high-dose polyethylene glycol administration has demonstrated equal efficacy with less invasiveness. Mineral oil is useful in lubricating hard stool and decreasing the pain associated with fissures, but it should not be given to infants or neurologically impaired patients because of the risk of aspiration and chemical pneumonitis. Dietary fiber supplements (ie, prebiotics), such as psyllium husk, guar gum, inulin, and fructosan, are helpful for maintenance therapy. Probiotics, notably the strains *Lactobacillus reuteri, L plantarum, Bifidobacterium longum, B breve,* and *B animalis* subsp *Lactis,* have also shown usefulness in the management of constipation.

The most important element in the management of functional constipation is persistence and long-term therapy. Six to 12 months of medication and follow-up are often necessary, because the colon must heal from a chronic injury to regain

Box 124.3. Dietary Therapy for the Management of Chronic Constipation

Avoid/Decrease

- Simple/Processed carbohydrates
  - Sugar
  - Corn syrup
  - Soda
  - White bread
  - White rice
  - Pastries/biscuits
  - Pasta/macaroni
  - Potato/corn chips
- Fat
  - Fried food
  - Saturated fat
  - Trans fat
  - Animal fat
  - Gravy
  - Vegetable oil
- Meat/Dairy
  - Processed meat
  - Red meat
  - Ground beef
  - Cold cuts
  - Cow's milk
  - Cheese
  - Cream

Introduce/Increase

- Fruit/Nectar
  - Pears
  - Plums
  - Papaya
  - Peaches
  - Pineapple
  - Apples
  - Berries
  - Cantaloupe
- Dried fruit
  - Prunes
  - Raisins
  - Apricots
  - Cranberries
  - Cherries
  - Dates
- Vegetables/Roots
  - Asparagus
  - Broccoli
  - Cauliflower
  - Carrots
  - Spinach
  - Yams
  - Parsnip
  - Celery
  - Beets
- Legumes/Tree nuts/Seeds
  - Red beans
  - Garbanzo beans
  - Peas
  - Cashews
  - Almonds
  - Walnuts
  - Pistachios
  - Sunflower seeds
  - Flaxseed

Box 124.4. Pharmaceutical and Supplement Therapy for the Management of Constipation

Osmotic Laxatives

- Polyethylene glycol
- Lactulose
- Magnesium hydroxide
- Phosphate

Psyllium Husk

- Bulking agents
- Guar gum
- Bran
- Calcium polycarbophil
- Methylcellulose

Prebiotics/Probiotics

- Inulin
- Fructo-oligosaccharide
- *Lactobacillus reuteri, L plantarum*
- *Bifidobacterium longum, B animalis, B breve*

Lubricant/Detergent

- Mineral oil
- Docusate sodium

Stimulants

- Senna
- Bisacodyl

Enemas/Suppositories

- Phosphate
- Saline
- Mineral oil
- Glycerin

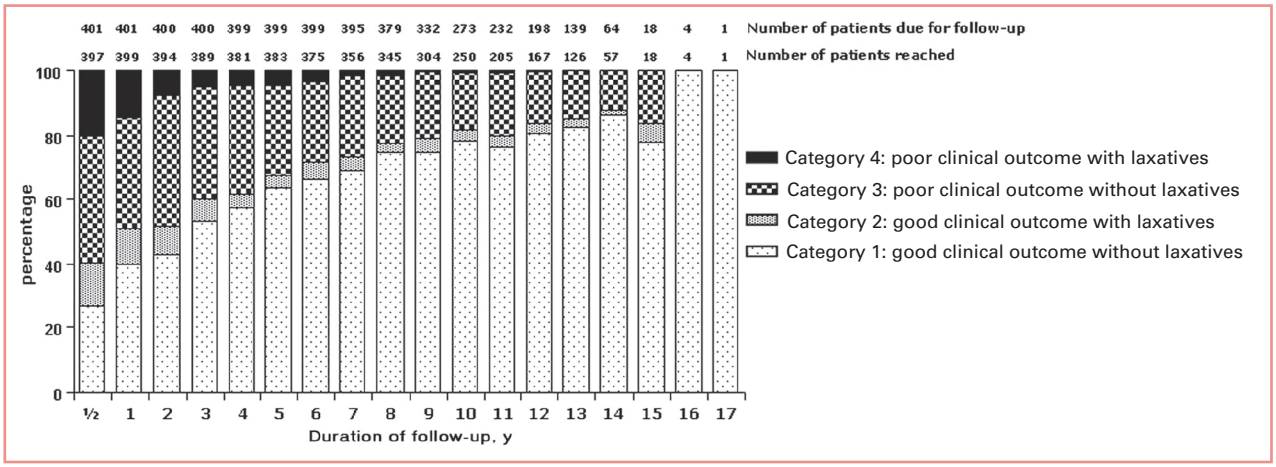

Figure 124.5. Clinical outcomes of pediatric patients treated for constipation according to follow-up year and outcome category.
Reprinted with permission from Bongers ME, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. *Pediatrics*. 2010;126[1]:e156–e162.

regularity and a normal caliber. Dietary changes and toilet hygiene should be incorporated into a healthy lifestyle and practiced into adulthood.

When to Refer to a Gastroenterologist

Constipation that is refractory to medical therapy should not be ignored. Although uncommon, anatomic aberrations (eg, malrotation), congenital megacolon, and intestinal pseudo-obstruction may manifest after infancy and cause toxic megacolon or intestinal or colonic volvulus, resulting in intestinal ischemia and devastation. These conditions may necessitate surgical intervention and long-term follow-up, and the affected patient should be referred to a specialist. Special attention should be paid to the infant with persistent constipation because of the high risk of serious conditions, such as congenital megacolon and malrotation.

Prognosis

Prognosis varies with etiology. Functional constipation usually is amenable to routine management, but treatment failures are reported in 20% of children with functional fecal retention, and some long-term studies suggest persistence of symptoms in 25% to 50% of children. A long delay in presentation increases the risk of poor clinical outcome. Age at presentation and stool frequency are also strong predictors of clinical outcome. The relapse rate at 1 year, after a successful initial intervention, is less than 5% but increases to 10% to 40% after 5 to 7 years, with significantly higher rates for women. Long duration of symptoms, poor self-esteem, and prior sexual abuse are among risk factors for a poor prognosis. Nonetheless, long-term studies support 2 important findings: prolonged laxative use is important initially, and dietary and behavioral modifications are ultimately successful in weaning laxative use (Figure 124.5).

CASE RESOLUTION

The child has functional constipation with a fissure. The bleeding is very distal, and bright red blood is noted on the toilet paper and in the bowl, not mixed into the stool. The belly pain is visceral, related to gas distention and stool retention, and relieved with defecation. Gassiness implies stool retention and fermentation in the colon. Normal appetite and growth parameters are reassuring. The rectal examination establishes the diagnosis of an anal fissure, and no further testing is necessary for this child at this time.

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CHAPTER 125

Abdominal Pain

George Gershman, MD

CASE STUDY

A 14-year-old boy is seen by his pediatrician for chronic pain in his epigastric area. According to the patient, he has experienced dull pain in the area since seventh grade, 2 years ago. Pain usually occurs about 1 hour after eating and at night. The pain is intense and lasts longer than an hour. He often drinks water or milk to alleviate the pain. He also reports frequent heartburn after spicy food but denies weight loss or diarrhea. The physical examination reveals abdominal tenderness in his epigastric area. The patient's bowel sounds are normal. There is no evidence of hepatosplenomegaly or ascites. A rectal examination shows a normal rectal vault and absence of a palpable mass. A stool guaiac test result is positive for occult blood.

Questions

1. What types of abdominal pain occur in children?
2. What characteristics distinguish functional from organic abdominal pain?
3. What are the common organic causes of recurrent abdominal pain in children?
4. What functional gastrointestinal disorders manifest with recurrent abdominal pain in children?

Abdominal pain, which may be acute or chronic, is among the most common symptoms of childhood and accounts for 2% to 4% of pediatric visits. Most children with acute abdominal pain have self-limiting conditions such as viral or bacterial gastroenteritis. However, a sudden onset of abdominal pain can be caused by serious, life-threatening conditions (eg, acute appendicitis, intussusception, hemolytic uremic syndrome). Chronic abdominal pain is among the most common chronic pain entities in children and adolescents, affecting an estimated 0.3% to 19% of children worldwide. Furthermore, chronic abdominal pain can have significant psychosocial and financial costs, which often persist into adulthood, making this a global health problem with an effect well beyond the individual child and family. In clinical practice, it is generally believed that pain that exceeds 2 months' duration can be considered chronic. Most children with chronic abdominal pain experience so-called functional abdominal pain (FAP). Over the last 20 years several functional gastrointestinal (GI) disorders associated with FAP have been established on a symptoms-based Rome classification system. In the latest version (Rome IV), a new category of FAP disorders has been included: FAP not otherwise specified (FAP-NOS), for children and adolescents whose symptoms do not match a specific FAP-associated disorder, such as functional dyspepsia, irritable bowel syndrome (IBS), or abdominal migraine. The diagnostic criteria for FAP-NOS must be fulfilled at least 4 times per month for a minimum of 2 months prior to diagnosis and include all of the following: episodic or continuous abdominal pain that does not occur solely during physiological events (eg, eating, menses); insufficient criteria for IBS, functional dyspepsia, or abdominal migraine; and after appropriate evaluation, abdominal pain that cannot be fully explained by any other medical condition.

An organic etiology is found in fewer than 10% of school-age children with chronic abdominal pain. However, failure to recognize the cause and/or delaying therapy can have devastating effects.

Epidemiology

Chronic abdominal pain is one of the most common symptoms in children, with a reported prevalence approaching 19%. Available data indicate an even higher prevalence of FAP disorders in school-age children in low-income countries. According to community- and school-based studies, up to 38% of children and adolescents experience abdominal pain weekly, with up to 24% of children reporting symptoms persisting longer than 8 weeks.

There is evidence to suggest a steady rise of abdominal pain symptoms in children approaching age 5 years and between ages 8 and 10 years.

There is no sex-related difference in the prevalence of abdominal pain until adolescence, when girls become more vulnerable to abdominal pain (the female to male ratio approaches 1.4:1).

Additional factors associated with a high prevalence of chronic abdominal pain are a positive family history and low socioeconomic status. Abdominal pain is an essential part of several functional GI disorders, such as IBS, functional dyspepsia, and abdominal migraine.

Pathophysiology

The 3 main causes of acute or chronic organic abdominal pain are inflammation, distention of the viscera, and ischemia.

Abdominal pain can originate from abdominal viscera (visceral pain), parietal peritoneum, abdominal wall, retroperitoneal skeletal

muscles (somatic pain), and extra-abdominal sites (so-called referred pain). Impulses of visceral pain are carried out primarily by small, unmyelinated, slow-conducting afferent C fibers incorporated into the autonomic sensory pathways. Each visceral organ receives dual sympathetic and parasympathetic innervations. Sensory fibers associated with the sympathetic nervous system traverse prevertebral (ie, celiac, superior, and inferior mesenteric ganglion) and paravertebral ganglion and terminate in the spinal cord. Sensory fibers contained in the vagus and pelvic nerves (ie, parasympathetic branch of the autonomic nervous system) terminate in the brain stem and lumbosacral spinal cord, respectively. Sensory fibers from visceral organs that connect with the spinal column terminate across 4 to 5 spinal segments, explaining why visceral pain is poorly localized and often perceived along the midline as a dull or aching sensation. For example, the onset of acute appendicitis is usually manifested by pain in the periumbilical or epigastric areas before the pain migrates to the right lower quadrant. It is frequently accompanied by symptoms of autonomic disturbance (eg, nausea, pallor).

Somatic pain is induced by irritation of parietal peritoneum and supportive tissue. The signals from the pain receptors (ie, nociceptors) are transmitted for the most part by rapid conducting myelinated A delta fibers responsible for tactile, thermal, and chemical stimulation and discrimination of location and intensity of stimuli. As a result, somatic pain is well localized, intense, and sharp. The important characteristic of somatic pain is aggravation by movement. Therefore, the child with somatic abdominal pain is likely to lie still, in contrast with the restless patient with visceral pain.

The classic example of referred pain is abdominal pain induced by inflammation of parietal pleura at the onset of pneumonia as the result of shared central projections of the parietal pleura and abdominal wall.

The location of abdominal pain is determined by the level of spinal cord connection with the corresponding visceral organs through the afferent sensory fibers. The structures of foregut origin, such as distal esophagus, stomach, duodenum, liver, and pancreas, are innervated by the nerves that enter the spinal cord at the level T5-9 segments. Pain from these organs is perceived between the xiphoid and umbilicus. The structures related to the primitive midgut (ie, small intestine, appendix, and right colon) project the afferent fibers to the T8-9 segments of the spinal cord. As a result, the associated pain affects the periumbilical area. The structures related to the embryonic hindgut, including the left colon and the rectum, share the innervations, which involve the spinal segments T10-L1 and allocate the pain between the umbilicus and symphysis pubis.

Radiation of the pain may help in diagnosis (eg, pain related to acute cholecystitis or biliary colic is often referred to the area just under the inferior angle of the right scapula or above the right clavicle). Another example of referred pain is pain between the scapulae and middle back region in patients with pancreatitis.

The pathophysiology of FAP is different from acute or chronic organic abdominal pain. The genesis of FAP is related to abnormalities in the enteric nervous system and dysregulation of the brain-gut interaction. Currently, it is believed that children with FAP may have abnormal responses to the normal physiological functions related to eating, such as intestinal distention during peristalsis, and hormonal changes during digestion. Functional abdominal pain may also be related to psychological conditions such as anxiety and parental separation.

Research data suggest that visceral hyperalgesia is the key element in the pathophysiology of FAP. This theory implies sensitization of the various receptors associated with afferent innervation of the GI tract by an infectious or allergic process or abnormal processing of afferent signals by the central nervous system.

Clinical Presentation

Children who experience abdominal pain may present with pain that may be characterized as persistent or intermittent, waxing and waning or steady and unrelenting, sharp or dull, and worsened or unaffected by movement. They may have associated symptoms, including vomiting, diarrhea, constipation, fever, weight loss, headache, and anorexia (Box 125.1).

Pain from distention of smooth muscle also waxes and wanes, is poorly localized, and is unaffected by motion. Distention of any hollow viscus, including the stomach, intestines, biliary tree, fallopian tubes, or ureters, can result in such symptomatology. A classic example of such pain is renal colic, from which the patient is writhing because of the discomfort.

Differential Diagnosis

In assessing the possible disease entities that may account for abdominal pain, patient age and duration of symptoms are the key differential components. The location of the pain may provide a clue to the etiology. Disease affecting the stomach is usually appreciated in the epigastrium. Duodenal problems are noted between the xiphoid and the umbilicus, small intestinal pathology is appreciated in the periumbilical area, and cecal inflammation may be felt from the epigastrium to McBurney point. Disease in the colon is less specifically noted but is usually felt in the hypogastrium. Pain related to the urinary bladder and rectum may project to suprapubic

Box 125.1. Diagnosis of Abdominal Pain in the Pediatric Patient

- Abdominal pain
- Abdominal wall rigidity
- Abdominal tenderness
- Vomiting
- Alterations in bowel sounds
- Diarrhea or constipation
- Anorexia
- Fever

or sacral areas. Pain may also be referred to the back. Renal colic is also noted in the back but more in a lateral or costovertebral angle site.

Acute and Chronic Abdominal Pain

Infants

Medical Conditions

A unique disorder of infants, infant colic has been referred to as paroxysmal fussiness of infancy and defined as prolonged, hard-to-soothe, and unexplained crying behavior (see Chapter 49). The onset of colic is usually between 2 and 4 weeks of age, with resolution by 3 to 4 months of age. Although colic has been attributed to recurrent abdominal pain, such pain has never been established as the cause of colic. Colic is characterized by fussiness and crying. Symptoms usually appear after feeding, particularly late in the day around family dinnertime. Infants cry, clench their fists, and flex their legs. A gas-cry-air-swallowing cycle seems to occur. The symptoms may respond to a number of measures, including rhythmic motion and anti-gas medications. Infants with colic usually appear well otherwise and often have accelerated weight gain secondary to repeated feeding made in efforts to soothe them.

Abdominal pain may also occur with food allergy, particularly cow's milk protein allergy. Generally, symptoms such as vomiting, diarrhea, stools positive for occult blood, failure to thrive, rhinitis, eczema, pallor, irritability, and a positive family history of allergies are associated findings. Disaccharidase deficiency (eg, lactose intolerance) may result in abdominal pain, but diarrhea is also usually present.

Surgical Conditions

Intussusception occurs most often in infants 6 months and older. The infant or toddler may have been previously well or have experienced a recent bout of diarrhea. Vomiting is reported in about 50% of patients, and pallor is frequently present. Lethargy is a not-uncommon associated symptom. An etiology is noted in fewer than 2.5% of affected infants, although a lead point (lymphoma or Meckel diverticulum) may be found in 5% to 10% of older children. The intussusception most often involves the area around the ileocecal valve. Compression of the vessels within the bowel wall may lead to necrosis and gangrene. The presence of blood and mucus in the stools gives a currant jelly appearance, although the initial stool is often normal, having been the stool that was present in the rectum prior to the intussusception.

The abdominal examination of affected children may be benign except for pain over the area of the intussusception or the presence of a mass. Bowel sounds may be increased secondary to the obstruction. A rectal examination may reveal blood and the presence of a mass. Fever and leukocytosis may also be noted. A flat radiograph of the abdomen is usually nonspecific. Intussusception is diagnosed by abdominal ultrasonography or barium enema. Hydrostatic reduction is the treatment of choice of intussusception; it is successful in almost 90% to 95% of children. Failure of hydrostatic reduction or associated complications is related to delayed diagnosis and severe edema and necrosis of the affected bowel. Surgical intervention is then required.

School-age Children

Medical Conditions

As noted previously, most children with chronic abdominal pain suffer from FAP disorders. By definition, abdominal pain in children with FAP-NOS is not affected by eating, defecation, menses, or other physiological functions. It may be triggered by a new environment, difficulties at school, or domestic problems. The pain is usually periumbilical and quite severe. It can be recurrent or continuous and may affect daily activity.

Abdominal pain in children with IBS is associated with changes in stool frequency and appearance, and pain that improves with defecation. Additional symptoms associated with IBS are increased frequency of stools (ie, ≥4 stools per day) or decreased stooling (ie, ≤2 stools per week), lumpy/hard or loose/watery stool, straining, urgency or feeling of incomplete evacuation, passage of mucus, and bloating or feeling of abdominal distention. Children with IBS are often anxious and experience multiple somatic symptoms.

Although many children seem to outgrow FAP and IBS, long-term follow-up studies suggest that a significant number remain symptomatic into adulthood.

Children with *functional dyspepsia* experience postprandial fullness, early satiety, nausea, vomiting, and epigastric pain.

Epigastric pain syndrome (1 of 2 subtypes of functional dyspepsia in the Rome IV classification) includes bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include burning quality of the pain but without a retrosternal component, and pain commonly induced or relieved by ingestion of a meal but that may also occur while fasting. Acid blockade with H_2-receptor antagonists and proton pump inhibitors can be offered for predominant symptoms of pain.

Abdominal migraine is characterized by recurrent paroxysmal episodes of intense, acute periumbilical, midline, or diffuse abdominal pain that lasts from 1 to several hours. Pain is often incapacitating. Children return to their usual state of health for weeks or months between the paroxysms of pain. The pain interferes with normal activities and is often accompanied by pallor, anorexia, photophobia, headache, nausea, and vomiting. There is an increased incidence of maternal migraine in children with abdominal migraine.

As mentioned previously, an organic etiology is found in fewer than 10% of school-age children with chronic abdominal pain. The symptoms and signs of organic diseases are persistent right upper and right lower quadrant pain, pain that awakens the child from sleep, dysphagia, persistent vomiting, arthritis, perirectal disease, GI blood loss, nocturnal diarrhea, involuntary weight loss, deceleration of linear growth, delayed puberty, unexplained fever, and

a family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease.

Peptic ulcers may develop in children in 3 circumstances. Acute infantile ulcers may occur in newborns secondary to stress and hypoxia. Stress ulcers may also occur in children who experience trauma, including burns and hypoxia (eg, after submersion). The routine uses of H_2-receptor antagonists or proton pump inhibitors has reduced the incidence of ulcers in hospitalized children who were critically ill.

The most common type of ulcer in children is acute, drug-induced ulcerations of the stomach and the duodenum caused by nonsteroidal anti-inflammatory drugs. Chronic peptic ulcers may develop in prepubertal children and teenagers with no apparent precipitating factors. A positive family history of peptic ulcer disease is reported in 25% to 50% of children. Unlike the classic ulcer symptoms of adults, in which pain occurs on an empty stomach and is relieved by eating, children may find that ulcer-related pain does not follow a specific clinical pattern. Positive family history, microcytic anemia, and stools positive for occult blood should raise clinical suspicion and prompt referral of the child to the pediatric gastroenterologist. There is clear evidence linking ulcer disease and infection with *Helicobacter pylori* in adults. The relationship between *H pylori* and peptic ulcer disease in children is less strong, although two-thirds of pediatric patients with endoscopic evidence of peptic ulcer disease have *H pylori* infection.

Mesenteric adenitis may produce symptoms indistinguishable from appendicitis, although affected children may not appear as ill as patients with acute appendicitis. Nausea and vomiting and a history of an antecedent upper respiratory infection are often present.

Infections such as tonsillitis or pneumonia may present with fever and abdominal pain. In addition, acute viral hepatitis could result in pain and tenderness localized to the right upper quadrant in association with anorexia. Young children with hepatitis A may be anicteric (see Chapter 127).

Pancreatitis produces abdominal pain that is often felt in the back. Historically, mumps was the most common cause of pancreatitis. Other infections, such as hepatitis B, Epstein-Barr virus, coxsackievirus B, and *Mycoplasma pneumoniae,* are the common infectious etiologies of acute pancreatitis.

Acute pancreatitis can be induced by some medications (eg, steroids, chemotherapeutic agents). Familial and recurrent forms of pancreatitis are also reported. Trauma, particularly from injuries sustained as a result of an impact against handlebars of bicycles, is a common cause. In children with pancreatitis and no apparent etiology, trauma related to child abuse should be considered.

Parasitic infestations, particularly with *Giardia intestinalis,* may produce abdominal pain, often with bloating and diarrhea.

Genitourinary problems may result in abdominal pain. An abnormal urinalysis provides clues to the etiology. Renal stones occur infrequently in children, and boys are more often affected than girls. In two-thirds of affected children, stones are detected incidentally or in association with a urinary tract infection. Stones may be composed of calcium phosphate or oxalate, magnesium, uric acid, cystine, or xanthine. In addition to flank or abdominal pain, patients may also experience hematuria, fever, recurrent urinary tract infection, and persistent pyuria.

Hematologic and vascular disorders, such as sickle cell disease, rheumatic fever, and Henoch-Schönlein purpura, may also present with abdominal pain. Sickle cell anemia should be considered in black children with abdominal pain. Pain may be related to vaso-occlusive events, including bowel ischemia and splenic infarction or cholecystitis. Henoch-Schönlein purpura, which is also referred to as anaphylactoid purpura, is characterized by a hemorrhagic skin rash, joint pain, and renal abnormalities in addition to abdominal pain. This pain may result from a number of processes, including vasculitis, inflammation and ischemia of the bowel wall, and intussusception of the small intestine.

Diabetes mellitus may precipitate to abdominal pain secondary to cramping of accessory muscles of respiration during a bout of ketoacidosis.

Acute intermittent porphyria is an uncommon cause of abdominal pain in children. The pain is often colicky and may be associated with constipation, nausea, and vomiting. Neurologic symptoms such as pain or paresthesia in the extremities may be present. Often, symptoms are precipitated by the ingestion of medications (eg, barbiturates, sulfa drugs). Some antispasmodic medications, such as Donnatal elixir, contain phenobarbital and can precipitate an attack. The diagnosis is made by evaluating the urine for the presence of protoporphyrin.

Primary peritonitis is secondary to infection with *Streptococcus pneumoniae* and is seen in children with nephrotic syndrome, cirrhosis, and sickle cell disease and in young girls with fever, abdominal pain, and vaginal discharge and no predisposing condition.

Surgical Conditions

Appendicitis is the most common surgical condition that produces abdominal pain in school-age children. Appendicitis may even occur in newborns, in whom it is seen in association with conditions that lead to diminished passage of stool, such as cystic fibrosis and Hirschsprung disease. The condition is frequently difficult to diagnose in children younger than 3 or 4 years for 2 reasons: examination of such young children for pain is difficult, and symptoms are similar to those of acute gastroenteritis (eg, fever, abdominal pain, anorexia). Classically, patients report periumbilical pain that localizes to the right lower quadrant in 1 to 5 hours. They often have a low-grade fever, with a temperature of 38°C (100.4°F). Vomiting and increased urinary frequency may occur. Stool consistency and pattern are variable (see Chapter 77).

The physical examination may reveal guarding and localized pain as well as rebound tenderness. A positive psoas or obturator sign may be present, indicating inflammation of these muscles. Tenderness may also be noted on rectal examination. Leukocytosis greater than 10,000/mL is also usually present. A radiograph of the abdomen may reveal 1 of 4 signs: a fecalith in the appendix (appendicolith), air in the cecum (sentinel loop), blurring of the shadow of the psoas muscle, or edema of the abdominal wall on the right side. A chest radiograph

is also useful to rule out the presence of pneumonia, which may produce symptoms that mimic appendicitis.

Meckel diverticulum may be responsible for abdominal pain in a number of ways. It may serve as the lead point for an intussusception, cause symptoms of ulcer disease (pain or hemorrhage) secondary to the presence of ectopic gastric mucosa, or become acutely inflamed as in appendicitis. Meckel diverticulum follows the rule of 2s: it affects 2% of the population, is 2 feet from the ileocecal valve, is 2 inches in length, and is 2 times more common in males than in females.

Adolescents

In female adolescents, gynecologic problems such as torsion of the ovary, mittelschmerz, dysmenorrhea, and pelvic inflammatory disease must be considered as causes of abdominal pain (see Chapter 61). In addition, pain may result from gall bladder disease secondary to cholelithiasis or cholecystitis. Cholelithiasis is also a consideration in adolescent patients with abdominal pain and fatty food intolerance who were previously pregnant.

Evaluation

History

A thorough history should be obtained (Box 125.2). A detailed description of pain may suggest a specific etiology. For example, pain worsened by eating can occur in children with gastroesophageal reflux disease, gastritis, cholecystitis, or pancreatitis. Nocturnal pain or pain relieved by a meal is more common in children with peptic ulcer disease. Pain relieved by defecation is suggestive of IBS. Pain aggravated by defecation raises suspicion of chronic inflammatory bowel disease. Localization of abdominal pain is an important additional diagnostic clue; FAP is usually localized along the midline or periumbilical area. Associated symptoms, such as fever, weight loss, anorexia, vomiting, diarrhea, leukocytosis, and an elevated sedimentation rate, also suggest an organic etiology.

Box 125.2. What to Ask

Abdominal Pain

- What is the nature of the pain? Is it sharp or dull, well or poorly localized, intermittent or relentless, worsened or unaffected by movement?
- How often does the pain occur?
- How long has the pain been present?
- Do any maneuvers, such as eating or lying down, reduce the symptomatology?
- Is the pain related to meals in any way? Is it worse after eating?
- Are any symptoms, such as fever, weight loss, anorexia, vomiting, diarrhea, constipation, dysuria, or headache, associated with the pain?
- Does anyone else in the family have similar symptoms?
- Does the pain occur at night and on weekends?
- Is there a history of travel?

Physical Examination

The physical examination should include an assessment of the severity of the pain. Children should be observed when they do not suspect that they are being watched. For example, a child who stands up and hops around when the physician leaves the room may have pain with a psychosomatic basis. Detection of abdominal tenderness may be ascertained during auscultation of the abdomen by pressing down with the stethoscope.

A rectal examination is also an integral part of the evaluation. In prepubescent girls with genitourinary symptoms or adolescent females, a genital assessment should be included.

Growth parameters should be evaluated for evidence of impairments, especially in children with recurrent abdominal pain. Abnormal findings such as abdominal masses or perianal skin tags are clues to an organic etiology. Children who appear vigilant and keep their eyes open during the examination often have organic problems.

Laboratory Tests

The laboratory assessment is determined by the differential diagnosis. In general, laboratory tests include a complete blood cell count, a urinalysis, and an erythrocyte sedimentation rate (in recurrent cases). In children with suspected lactose intolerance, a hydrogen breath test is recommended by some physicians, although a trial of dietary manipulation or use of exogenous lactase (eg, Lactaid, Lactase Enzyme) may be more cost-effective. Other laboratory tests, such as serum amylase or liver function studies, are appropriate if pancreatitis or hepatitis is suspected. Detection of *H pylori* antigen in the stool supports the diagnosis of *H pylori* infection. Stool evaluation for occult blood and parasites is also helpful. Consultation with a gastroenterologist should be considered in patients suspected of having peptic ulcer disease or inflammatory bowel disease. Gastroenterologists may perform diagnostic procedures (eg, endoscopy) to arrive at the diagnosis.

Imaging Studies

In general, a flat radiograph of the abdomen should be obtained, especially if an acute surgical condition is suspected. Ultrasonography or abdominal computed tomography can be useful in some children with right low quadrant pain to confirm the diagnosis of acute appendicitis. Abdominal ultrasonography and a barium enema are indicated to diagnose intussusception. Technetium scans help detect Meckel diverticulum if ectopic gastric mucosa is present. Ultrasonography is useful in suspected cases of cholelithiasis and cholecystitis. It may also detect pancreatic edema or pseudocyst, hydronephrosis, or abdominal masses. Upper GI endoscopy is very useful for patients with red flag symptoms.

Management

The management of abdominal pain in children depends on the suspected cause. Children with peptic ulcer and concomitant *H pylori* infection require triple or quadruple therapy with proton pump inhibitors and antimicrobial agents. Children with celiac disease

improve on a gluten-free diet, and those with lactose intolerance improve by avoiding lactose or ingesting lactase tablets with meals.

The management of FAP disorders in children is more challenging. The first obstacle is the lack of data related to the efficacy of pharmacological and behavioral therapy in children. The second is a very high placebo response rate in nearly all clinical trials in adults, ranging from 16% to 70% (average, 40%); there is no reason to believe this would be different in children.

Currently, the treatment of children with FAP begins with support and empathy for the family and assurance that the child is not seriously ill and will most likely outgrow the pain. With this approach, up to 75% of patients have resolution of their symptoms. However, patients with more severe illness will require a multidisciplinary approach, including education, identification and modification of physical and psychological stress factors, dietary interventions, and pharmacological and psychological therapies.

Prognosis

In general, the prognosis for children with acute abdominal pain is good, although it varies depending on the condition. In 30% to 50% of children with chronic abdominal pain, the symptoms often resolve within 2 to 6 weeks of diagnosis. Thirty percent to 50% of affected children experience abdominal pain as adults, although the pain does not limit their activities. As adults, these individuals may experience IBS or other chronic nonspecific symptoms, such as headache, backache, and chronic pelvic pain.

CASE RESOLUTION

The patient has symptoms suggestive of peptic ulcer disease. Although less common in pediatric patients than in adults, postprandial epigastric abdominal pain improved by eating, along with a family history, should raise suspicion for peptic ulcer disease, which is often associated with gastroesophageal reflux and chronic gastritis. Male teenagers are affected more frequently than female adolescents. Esophagogastroduodenoscopy is the standard diagnostic method. The patient has evidence of peptic ulcer disease on endoscopy along with *H pylori* infection. He is started on triple therapy, including proton pump inhibitor and 2 antibiotics for 10 days, followed by 2 months of acid suppression medications. On follow-up, the patient's symptoms had fully resolved.

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CHAPTER 126

Jaundice

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CASE STUDY

A 4-week-old boy is brought to the office for a routine weight check because he is breastfeeding. He was the product of a full-term, normal, spontaneous vaginal delivery, with a birth weight of 3,600 g (7 lb, 15 oz). He has been feeding well, exclusively at the breast, with loose stools after each feeding. On physical examination, the infant weighs 4,900 g (10 lb, 13 oz). The examination is normal except that the boy appears jaundiced. On further questioning, the mother states that her son was jaundiced shortly after birth, but she was told that the bilirubin level was all right. She thinks the jaundice may be more noticeable now. His stool is yellow and pasty, although sometimes it appears lighter in color.

Questions

1. What are the common causes of unconjugated hyperbilirubinemia in young infants?
2. What are the common causes of conjugated hyperbilirubinemia in young infants?
3. What are the usual causes of jaundice in older children and adolescents?
4. What is the appropriate management of hyperbilirubinemia in breastfed infants?
5. What diagnostic studies are done to determine the etiology of jaundice?

Jaundice occurs when bilirubin reaches a level in the blood that makes it visibly apparent. In newborns, this level is 5 mg/dL. In older children and adolescents, jaundice becomes apparent at serum bilirubin levels of 2 mg/dL. The term *physiologic jaundice* is used to denote the jaundice that normally occurs after birth. In full-term neonates, bilirubin reaches its peak of approximately 6 mg/dL between the second and fourth days after birth. Levels above 10 mg/dL likely are not physiologic. Typically, bilirubin returns to a normal level (≤1 mg/dL) by 12 days of age. Preterm newborns experience their peak level of bilirubin, which may be up to 10 to 12 mg/dL, between the fifth and seventh days after birth. Levels above 14 mg/dL are probably not physiological. Levels may be elevated in preterm neonates for up to 2 months.

Physiologic jaundice is a benign finding that affects all newborns; however, other, more serious disorders may present with jaundice in the newborn period. The physician must be able to differentiate between physiologic and pathologic causes of jaundice to ensure appropriate intervention and management. New-onset jaundice in older children and adolescents is never physiologic; the natural history is determined by the underlying disorder.

Epidemiology

Physiologic jaundice is nearly universal in neonates because of the rapid turnover of red blood cells and the relative immaturity of the liver, which give rise to unconjugated hyperbilirubinemia. The most notable disorder associated with increased levels of unconjugated bilirubin in the newborn period is hemolysis from maternal antibodies to the neonate's blood group (eg, ABO incompatibility). *Breastfeeding jaundice* results from inadequate milk intake, mild dehydration, and mild elevation in the level of conjugated bilirubin. The condition should be distinguished from pathologic cholestasis. Breast milk jaundice is different from breastfeeding jaundice and affects approximately 1% of newborns and infants fed breast milk exclusively. Factors in the breast milk as well as the immature neonatal microflora that promote recirculation of bilirubin from the gut (ie, enterohepatic circulation) give rise to unconjugated hyperbilirubinemia. Various illnesses, particularly bacterial infections, also may precipitate jaundice in newborns. *Cholestasis*, which is defined physiologically as a reduction in canalicular bile flow, manifests as conjugated hyperbilirubinemia. Neonatal cholestasis, which occurs in a small number of patients with neonatal jaundice, may be caused by neonatal hepatitis (often without a discernible cause), extrahepatic biliary atresia (BA), or genetic and metabolic diseases. Jaundice occurs much less frequently in the postneonatal period and is most often secondary to viral hepatitis (see Chapter 127).

Clinical Presentation

Children with jaundice have yellow skin, conjunctiva, and mucous membranes. In newborns, the coloration may not be appreciated by parents or caregivers because of its gradual onset and the inexperience of the parents or caregivers. The finding may be apparent in otherwise asymptomatic newborns and infants during routine health maintenance visits but may go unappreciated by the examining physician. In addition to the yellow color, the child with jaundice also may present with symptoms related to the cause of the jaundice, including vomiting, anorexia, failure to thrive, acholic (ie, pale, poorly pigmented) stools, dark urine, fatigue, and abdominal pain or fullness, and rickets (Box 126.1).

Box 126.1. Diagnosis of Jaundice in the Pediatric Patient

- Yellow skin, mucous membranes, and conjunctiva
- Tenderness in the right upper quadrant of the abdomen
- Hepatomegaly
- Anorexia
- Acholic stools
- Vomiting
- Pruritus

Pathophysiology

Bilirubin, a red pigment found primarily in bile, forms from the breakdown of heme-containing compounds, mainly hemoglobin, but also muscle myoglobin, cytochromes, catalases, and tryptophan 2,3-dioxygenase. Disruption along any point in the synthesis and transport of bilirubin or anatomic obstruction in the processing and excretion of bile may result in increased levels of bilirubin and the appearance of jaundice (Figure 126.1). After the breakdown of hemoglobin, unconjugated bilirubin is taken up by the hepatocyte plasma membrane carrier, bilitranslocase, and bound to intracellular proteins (Y proteins or glutathione *S*-transferase). Uptake depends on hepatic blood flow and the presence of the necessary binding proteins. Once in the liver, unconjugated bilirubin is conjugated by the enzyme glucuronosyltransferase. Conjugated bilirubin, which is water soluble, can be eliminated through the kidneys; unconjugated bilirubin is not water soluble and can be taken up in tissues and stored. After conjugation, bilirubin passes into the bile through the bile canaliculi. It then moves to the gastrointestinal tract, where some of it may be reabsorbed (ie, enterohepatic circulation) or acted on by bacteria to form urobilinogen and stercobilinogen, which may appear in the urine or stool, respectively.

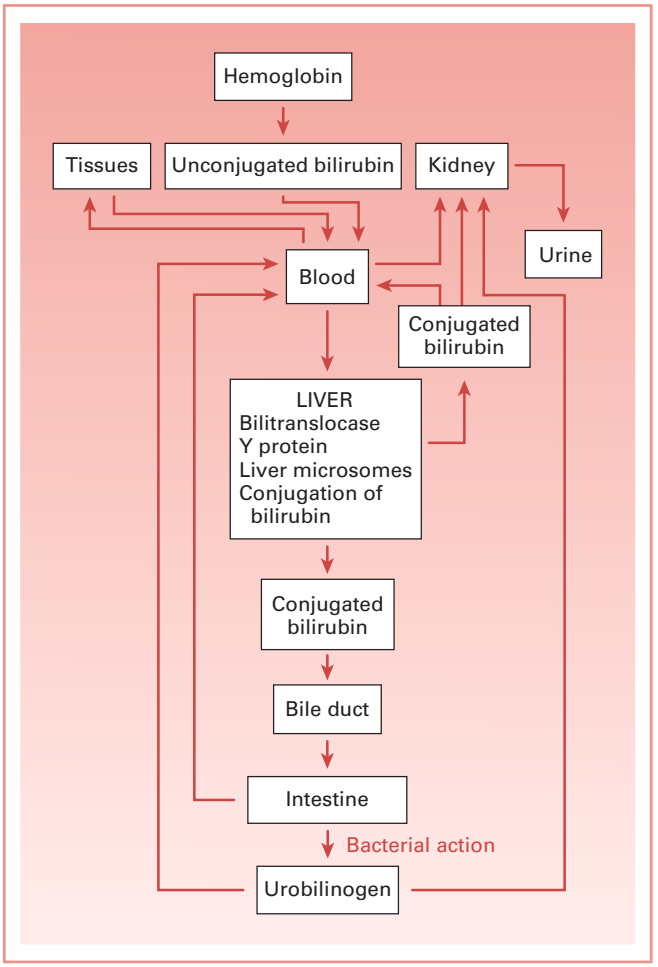

Figure 126.1. The bilirubin pathway.

In neonates, several factors contribute to physiologic jaundice. First, increased destruction of red blood cells occurs, because red blood cell survival in neonates is only 70 to 90 days, compared with 120 days in older children and adults. Second, hepatic uptake is lower, likely a result of decreased levels of hepatic proteins as well as decreased hepatic blood flow. Levels of glucuronosyltransferase do not reach adult values until the second week after birth; as a result, conjugation of bilirubin occurs at a slower rate. *Gilbert syndrome* is an autosomal recessive disorder characterized by low physiologic levels of glucuronosyltransferase; these individuals remain prone to jaundice at times of illness, stress, and starvation. Prolonged jaundice may occur in some breastfed newborns and infants and is likely related to poor caloric or fluid intake, weight loss and catabolism, slow passage of meconium, or immature intestinal microflora. Breast milk jaundice is different. It is an unconjugated hyperbilirubinemia and is thought to result from milk components such as pregnanetriol, which blocks glucuronosyltransferase. (See Chapter 29 for more information on breastfeeding.) In older children, similar mechanisms may act to cause an increase in the bilirubin level in disease states. Hemolytic anemias (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency, pyruvate kinase deficiency [PKD]) may result in increased red blood cell destruction. Inflammatory or infectious processes involving the liver, such as hepatitis, may impair the ability of the liver to excrete bilirubin. Pharmaceutical and toxicologic agents may also interfere with the ability of the liver to metabolize bilirubin.

Differential Diagnosis

The differential diagnosis of jaundice in children involves 3 criteria: age, the type of hyperbilirubinemia (conjugated or unconjugated), and, if the hyperbilirubinemia is conjugated, the nature of the obstruction (intrahepatic or extrahepatic). The latter 2 factors are particularly important in determining the etiology of jaundice in neonates and young infants. A diagrammatic representation of the differential diagnosis of jaundice in children is shown in Figures 126.2, 126.3, and 126.4.

Neonates and Infants Younger Than 8 Weeks

Unconjugated Hyperbilirubinemia

Jaundice occurs universally in all newborns; however, marked elevation of bilirubin levels (≥15 mg/dL) and the presence of jaundice in the first 24 hours after birth or beyond 2 weeks of age warrant

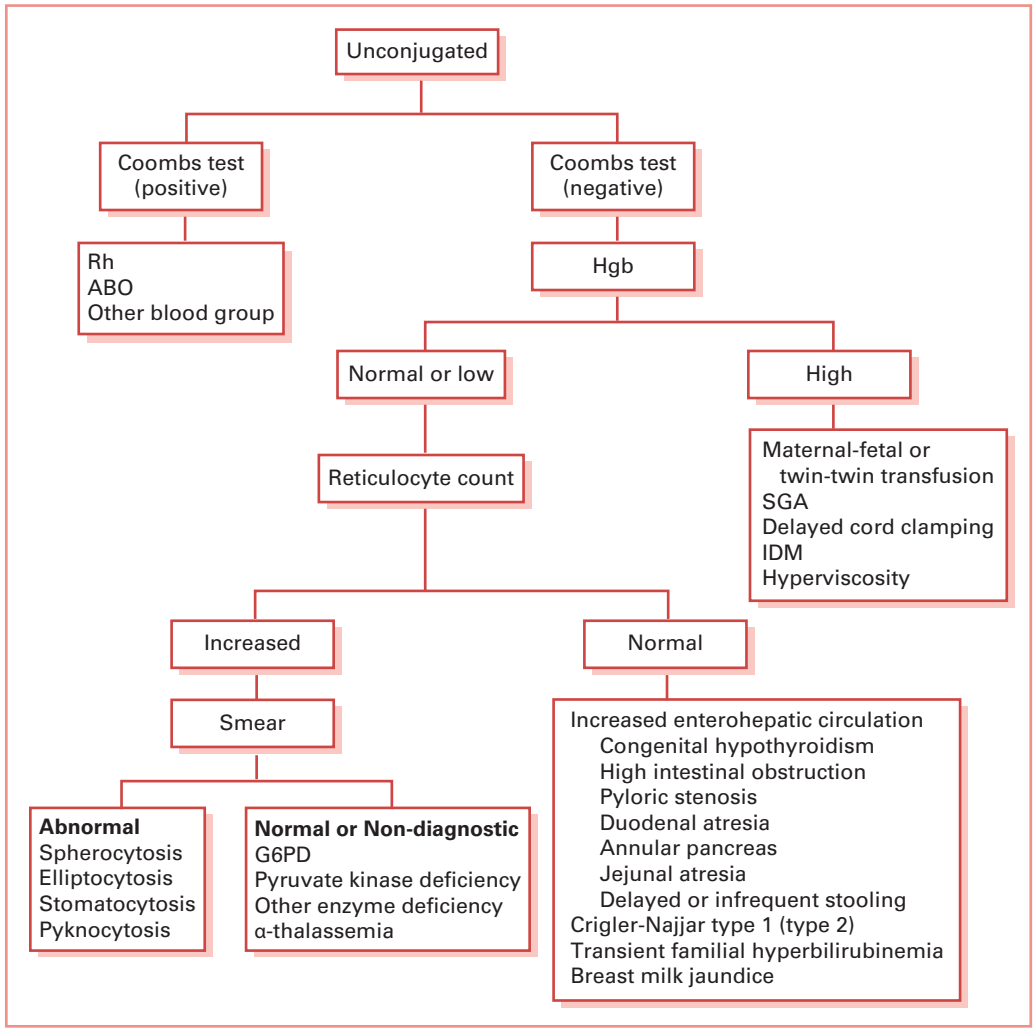

Figure 126.2. Differential diagnosis of jaundice (unconjugated hyperbilirubinemia) in neonates and infants through age 8 weeks.

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; Hgb, hemoglobin; IDM, infant of diabetic mother; SGA, small for gestational age.

assessment. When less than 15% of the total bilirubin is conjugated (direct hyperbilirubinemia), unconjugated hyperbilirubinemia is present. This is determined by measuring the levels of total and direct (ie, conjugated) bilirubin in the blood (bilirubin fractionation). Physiologic jaundice is associated with unconjugated hyperbilirubinemia and typically does not require an evaluation. The hematologic workup of affected newborns and infants is normal. *Breastfeeding jaundice* secondary to inadequate human milk intake may resemble physiologic jaundice and occurs during the first week after birth. With *breast milk jaundice,* bilirubin levels rise during the second week after birth when physiologic jaundice is improving. Breast milk jaundice usually peaks by age 4 weeks and can last up to 12 weeks. Levels may reach as high as 25 to 30 mg/dL, possibly posing a threat to the developing brain. In those cases, it may be necessary to stop breastfeeding and introduce formula or phototherapy.

Conditions associated with slow intestinal transit time and increased enterohepatic circulation, such as hypothyroidism, also may result in jaundice. High intestinal obstructions, such as pyloric stenosis, duodenal atresia, annular pancreas, and jejunal atresia, may cause jaundice, perhaps because of starvation and decreased levels of glucuronosyltransferase. Genetic and hematologic disorders should also be considered in the differential diagnosis.

Crigler-Najjar syndrome type 1 is an autosomal recessive disorder characterized by an absence of glucuronosyltransferase and, thus, severe unconjugated hyperbilirubinemia with bilirubin levels approaching 50 mg/dL soon after birth. *Crigler-Najjar syndrome type 2* is also autosomal recessive but is characterized by a reduced function of glucuronosyltransferase; bilirubin levels average 20 mg/dL and persist beyond 2 weeks in the absence of hemolysis. Because of very high bilirubin levels, type 1 disease may result in kernicterus unless managed with exchange transfusion. Phototherapy, cholestyramine resin, and eventual liver transplantation are additional therapies that may be necessary. Hematologic problems may also produce jaundice in the neonatal period. Such problems are most often associated with blood group (usually Rh or ABO) incompatibility

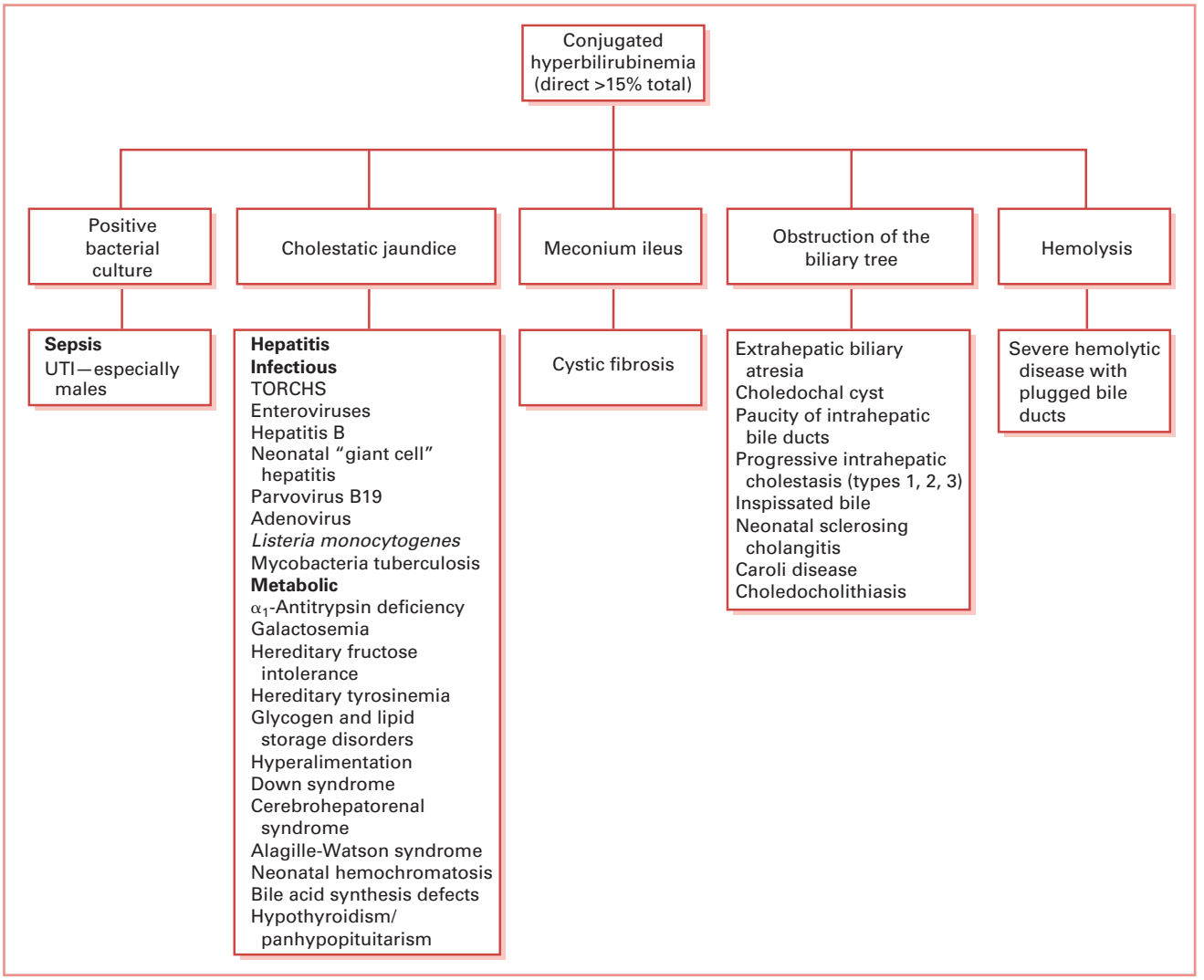

Figure 126.3. Differential diagnosis of jaundice (conjugated hyperbilirubinemia) in infants (during the first 8 weeks after birth).
Abbreviation: TORCHS, toxoplasmosis, other agents (syphilis, hepatitis B, varicellazoster virus, human immunodeficiency virus, parvovirus B19, enteroviruses, lymphocytic choriomeningitic virus), rubella, cytomegalovirus, and herpes simplex virus.

between mothers and newborns, but some minor blood group antigens can also precipitate jaundice. Jaundice occurs in affected newborns and infants because of the rapid destruction of red blood cells, which release hemoglobin that converts to bilirubin. Hemolytic anemias, such as spherocytosis, result in jaundice, as do conditions that result in polycythemia (ie, increased red blood cells in the circulation), such as maternal-neonate or twin-twin transfusions, neonates who are small for gestational age, delayed clamping of the umbilical cord, infants of diabetic mothers, and neonates with hyperviscosity syndrome.

Conjugated Hyperbilirubinemia

When more than 15% of the total bilirubin is direct, jaundice is categorized as conjugated (ie, direct) hyperbilirubinemia. This is always pathologic and warrants further investigation. Total parenteral nutrition is the most common cause of conjugated hyperbilirubinemia in the neonatal intensive care unit. It is most likely related to the lipid component of the total parenteral nutrition; however, it does not usually present a diagnostic dilemma. The institution of oral feedings helps reverse the process. In other cases, determining whether the problem is intrahepatic or extrahepatic is paramount. Intrahepatic involvement represents a spectrum of conditions from inflammation (ie, hepatitis), to inadequate formation of the bile ducts (ie, biliary hypoplasia, Alagille syndrome), to the destruction of the bile ducts (ie, BA).

Hepatitis is inflammation of the liver and usually is caused by an infection in the liver, although infection elsewhere in the body (eg, sepsis, urinary tract infection in neonates and young infants) may also cause jaundice. Urinary tract infections are usually caused by *Escherichia coli.* The hepatic involvement resolves with appropriate antibiotic therapy of the primary infection.

Primary liver infection in the neonatal period may be caused by a number of pathogens, collectively abbreviated as TORCHS (toxoplasmosis, other agents, rubella, cytomegalovirus [CMV], human herpesvirus, HIV, syphilis); the most common culprits are CMV and human herpesvirus. Neonates who are infected prenatally often have low birth weights, hepatosplenomegaly, petechial rashes, and ocular

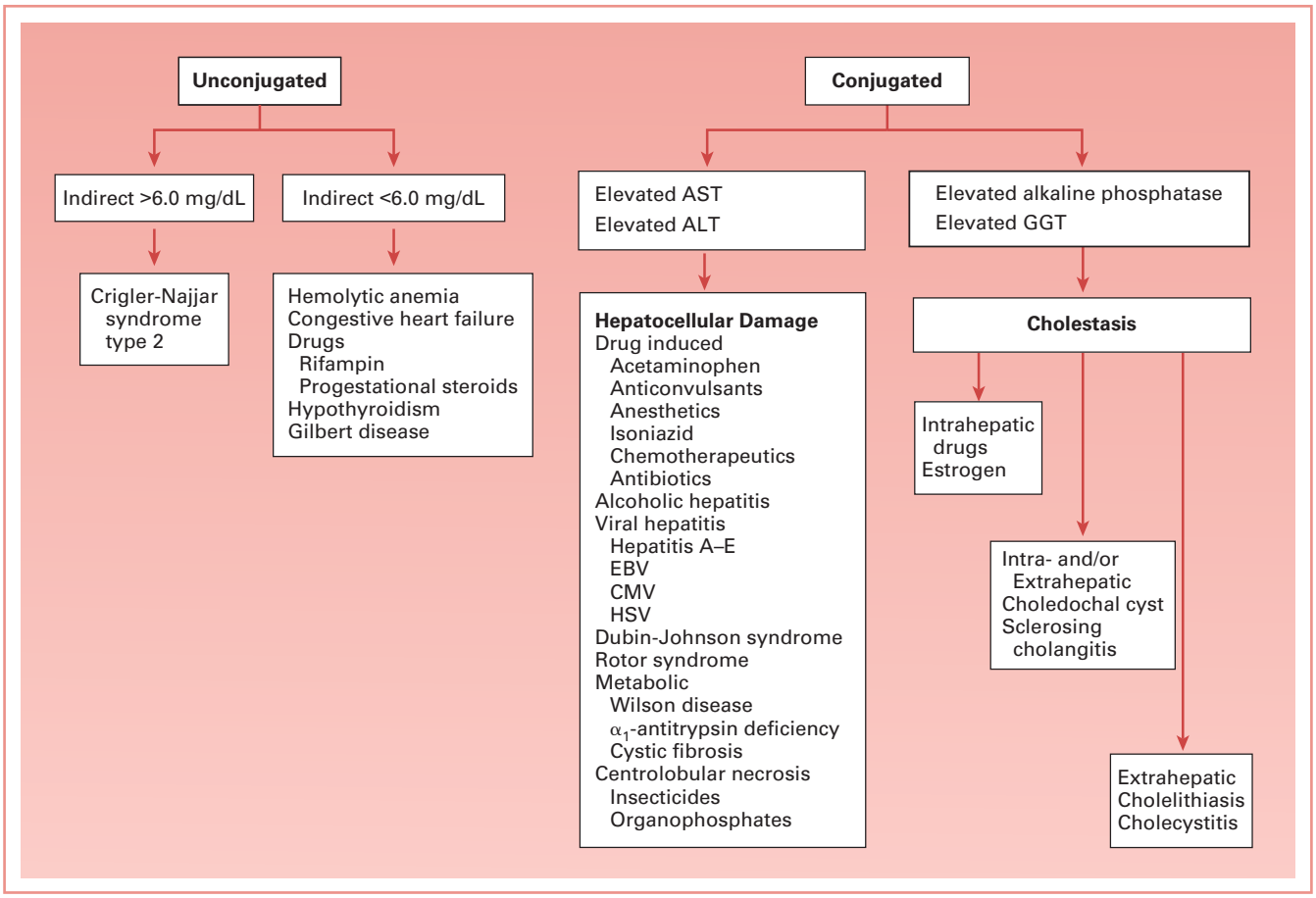

Figure 126.4. Differential diagnosis of jaundice in older infants, children, and adolescents.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GGT, γ-glutamyltransferase; HSV, herpes simplex virus.

findings, such as cataracts and chorioretinitis. Maternal transmission of hepatitis B is a possible etiology of neonatal cholestasis, but hepatitis C is usually asymptomatic in the neonate. Hepatitis A may cause an acute infection but rarely manifests as jaundice in neonates. Other infectious causes include enteroviruses, reovirus type 3, human parvovirus B19, human herpesvirus 6, human adenovirus 2, *Listeria monocytogenes*, and tuberculosis. Typically, these conditions are differentiated based on culture, polymerase chain reaction, or serology testing. Certain physical and epidemiologic findings may help distinguish these entities. For example, syphilis is more common in developing nations than in developed nations and jaundice may appear within the first 24 hours after birth or later on in infancy. Infection with *L monocytogenes* may be associated with the presence of focal granulomas on the posterior pharynx; similar granulomas may be evident in the liver.

Metabolic diseases and inborn errors of metabolism may also cause hepatitis. Most of these conditions are inherited in an autosomal recessive manner and are relatively rare. Newborns and infants may present with vomiting, irritability, lethargy, anorexia, hepatomegaly, hypoglycemia, failure to thrive, bleeding, or cataracts in addition to jaundice. Galactosemia may be detected through neonatal screening or may present as *E coli* sepsis. Newborns and infants with hereditary fructose intolerance present after exposure to fructose, sucrose, or sorbitol, usually past the neonatal period. Depending on the population, α_1-antitrypsin deficiency may account for 20% to 30% of cases of idiopathic neonatal liver disease and up to 10% of neonatal cholestatic disease. Inborn errors of metabolism (eg, glycogen storage disease, tyrosinemia) generally present with conjugated (direct) hyperbilirubinemia, whereas inborn errors of erythrocyte metabolism (eg, PKD or G6PD deficiency) present with unconjugated (indirect) hyperbilirubinemia.

Other genetic conditions that cause jaundice in newborns include lysosomal storage disease (eg, type 2 [infantile] Gaucher disease, Niemann-Pick disease, Wolman disease) and cystic fibrosis. The latter can cause cholestatic jaundice because of the presence of inspissated bile in the bile canaliculi. Approximately 50% of newborns and infants with cystic fibrosis have meconium ileus, meconium peritonitis, or intestinal atresia. "Plugged" bile ducts, resulting from bilirubin production overwhelming the drainage system, may occur with severe hemolytic anemia as well. Drugs may also induce intrahepatic cholestasis. Several syndromes are associated with persistent intrahepatic cholestasis. Alagille syndrome (ie, arteriohepatic dysplasia) is characterized by dysmorphic facies, skeletal and cardiovascular anomalies, and a paucity of intralobular bile ducts; the prevalence is 1 in 100,000 live births. Progressive familial intrahepatic cholestasis (which typically results from autosomal recessive defects

in bile acid transporters) and bile acid synthesis defect, together with Alagille syndrome (which is autosomal dominant), account for a total of approximately 10% of cases of neonatal cholestasis. Not surprisingly, as the etiologies for more of these cases are identified through genetic and metabolic testing, fewer cases are labeled "idiopathic neonatal hepatitis."

Extrahepatic BA accounts for approximately 25% of cases of cholestasis in newborns and is characterized by ascending obliteration of the biliary tree. Often, newborns and infants are well until 3 to 6 weeks of age, when they develop conjugated (direct) hyperbilirubinemia. The prevalence is 1 in 14,000 live births, and diagnosis must be prompt for long-term success of surgical correction. Surgery after 2 months of age is associated with liver failure and the future need for transplantation. It has been postulated that some primary insults, such as α_1-antitrypsin deficiency, metabolic disorders, or viral infections (eg, CMV, human herpesvirus), may be the inciting event resulting in BA. Choledochal cysts appear as dilatations of the biliary tree and obstruct the passage of bile. They usually present after the perinatal period with bilious emesis.

Older Infants, Children, and Adolescents

The approach to the differential diagnosis of jaundice in older infants and children is similar to that for neonates and young infants. The differential diagnosis is suggested by the total bilirubin level and the fractionated components. Unconjugated hyperbilirubinemia is usually caused by hemolysis, and the level of indirect bilirubin helps clarify the differential diagnosis. Patients with levels below 6 mg/dL may have hemolytic anemia; haptoglobin testing and a peripheral blood smear should help solidify the diagnosis. Patients with an indirect bilirubin level greater than 6 mg/dL may have Crigler-Najjar syndrome type 2; such patients respond favorably to phenobarbital. Congestive heart failure and hypothyroidism may also produce unconjugated hyperbilirubinemia to varying degrees. Gilbert disease is the most common inherited cause of unconjugated hyperbilirubinemia, with a prevalence of 5%; it is caused by reduced activity of the enzyme glucuronosyltransferase, which conjugates bilirubin. Bilirubin levels may rise to approximately 5 mg/dL in response to stress and starvation. Many different drugs, including rifampin and birth control pills, may also be associated with hyperbilirubinemia (usually indirect).

Conjugated (direct) hyperbilirubinemia may result from cholestasis and hepatocellular inflammation or injury. Cholestasis is characterized by high levels of alkaline phosphatase, mild to moderate elevation of transaminase levels, and increased levels of γ-glutamyltransferase. Intrahepatic cholestasis can occur in relation to drugs (ie, estrogens) and alcohol, as well as genetic disorders, such as progressive familial intrahepatic cholestasis (PFIC). This condition is divided into types 1, 2, and 3, depending on gene involvement. In PFIC, the capacity for liver cells to secrete bile is reduced. Extrahepatic cholestasis occurs with cholelithiasis or other obstructions of the biliary tree, such as a cyst. Cholelithiasis may occur in individuals with hemolytic anemia (black or brown pigment gallstones) and in adolescents who are overweight or postpartum (usually cholesterol gallstones). Hepatocellular injury most often results from hepatitis (see Chapter 127), including the infectious, alcoholic, nonalcoholic steatohepatitis, and drug-induced forms. Rarer disorders include Dubin-Johnson and Rotor syndromes. Metabolic diseases, such as Wilson disease, α_1-antitrypsin deficiency, and cystic fibrosis, should be considered in the differential diagnosis of every older child who presents with direct (conjugated) hyperbilirubinemia.

Evaluation

History

A careful history must be obtained, documenting the timing of the onset of jaundice, presence of fever (suggestive of infection), feeding intolerance, pale stools (suggestive of obstruction), and growth and development (Box 126.2).

Physical Examination

The patient should be evaluated for evidence of dysmorphism, organomegaly of the liver or spleen, ocular anomalies, developmental delay, abnormal heart sounds (eg, murmur), rash, hearing deficits, or lymphadenopathy. Unique facial features (eg, micrognathia, ocular anomalies) or a cardiac defect may be suggestive of a genetic disorder, such as PFIC or Alagille syndrome. Spleen enlargement is noted in hemolytic disorders and some inborn errors of metabolism, whereas isolated liver enlargement is suggestive of hepatitis. Rashes and lymphadenopathy are associated with certain infectious conditions, including congenital infections (eg, TORCHS) in newborns and infectious mononucleosis in adolescents.

Laboratory Tests

In the newborn nursery, noninvasive methods are used to measure the level of jaundice. The bilirubin meter uses reflectance spectrophotometry to determine the skin color and strongly correlates with serum bilirubin levels. Another noninvasive method is the

Box 126.2. What to Ask

Jaundice

- What associated symptoms are present?
- How long have the symptoms been present?
- Does the child have a fever?
- What is the color of the stools?
- Is there a family history of jaundice, hepatitis, or consanguinity?
- What is the child's diet? If a newborn or an infant, is the child fed mother's milk or formula?
- When did the parents or caregivers first notice the jaundice?
- Has the child been jaundiced previously?
- Has the child been vaccinated against hepatitis A and B?
- Is there a history of foreign travel or shellfish ingestion?
- Was newborn screening performed, and are the results known?

icterometer, which has an acrylic plastic color chart that is placed against the neonate's nose.

The aim of the laboratory assessment is to discover where bilirubin metabolism is abnormal. Total bilirubin as well as fractionated bilirubin levels should be determined. If the levels of direct (conjugated) bilirubin are elevated, consultation with a pediatric gastroenterologist should be considered. Demonstration of a yellow color to the foam of a shaken specimen of urine correlates with the presence of conjugated hyperbilirubinemia. Urine test strips also readily detect conjugated bilirubin in the urine.

In the child with unconjugated hyperbilirubinemia, hemolytic anemia is diagnosed based on a complete blood cell count with reticulocyte count and evaluation of the peripheral smear. Normal or low hemoglobin is typical in hemolytic anemia. An elevated reticulocyte count or an abnormal peripheral blood smear is indicative of hemolysis. Hemolytic anemias with abnormal peripheral smears include spherocytosis, elliptocytosis, stomatocytosis, and pyknocytosis (see Chapter 98). The levels of serum haptoglobin, which binds free hemoglobin, thereby decreasing its oxidative activity, are diminished in hemolytic disorders. In the neonate, a hemoglobin level should be obtained, an antiglobulin (ie, Coombs) test should be performed, and newborn and maternal blood types should be determined. In the child with conjugated hyperbilirubinemia, tests should be performed to determine if an infection such as bacteremia, urinary tract infection, congenital infection (eg, TORCHS), or hepatitis is present. Evaluation for metabolic diseases should also be obtained by assessing urine for the presence of reducing substances, organic acids, and bile acid metabolites. A sweat chloride test and assessment of α_1-antitrypsin level should be considered. The status of liver function can be determined by evaluating aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, and alkaline phosphatase. To assess synthetic liver function, the physician should test prothrombin time, total protein, albumin, glucose, cholesterol, and ammonia.

Imaging Studies

The anatomy of the biliary tree can be evaluated on ultrasonography, which usually is sufficiently sensitive to visualize a choledochal cyst. A "triangular cord sign" is a specific but not very sensitive sign seen on ultrasonography for the diagnosis of BA. A triangular-shaped echogenicity demonstrates the atretic ductal remnant in the area cephalad to the portal vein bifurcation. Other imaging tests, including excretion studies (eg, biliary scintigraphy by radioisotope [ie, hepatobiliary iminodiacetic acid scanning]) and cholangiography, can be used to help differentiate hepatitis from BA. Consultation with a pediatric gastroenterologist or pediatric surgeon may be appropriate.

Liver Biopsy

A histologic evaluation may be necessary if the etiology cannot be determined based on laboratory results. A detailed review by an experienced pathologist may be diagnostic and save the neonate from exploratory surgery.

Management

The management of jaundice depends on the cause of the condition. Physiologic jaundice and jaundice secondary to breastfeeding usually require no intervention. Breastfeeding jaundice is potentially preventable. The mother should be advised to initiate breastfeeding within 1 hour after birth with continuous rooming-in, continue to breastfeed every 2 to 3 hours, and promptly respond to hunger cues. Supplementation with water or sugar water should be discouraged. Neonatal urine output should be monitored. If bilirubin levels are greater than 20 mg/dL, interrupting breastfeeding for 24 to 48 hours will successfully lower bilirubin levels; however, support and counseling are mandatory to ensure that breastfeeding resumes. Studies suggest that the use of a casein hydrolysate formula (eg, Nutramigen, Alimentum) may result in a greater degree of reduction in the level of bilirubin than the use of a whey-predominant formula (eg, Enfamil, Similac). Some physicians use bilirubin-reducing lights to prevent kernicterus, but available data do not support imminent neurologic damage even when bilirubin levels climb as high as 25 to 30 mg/dL. Newer phototherapy techniques involve the use of woven fiber-optic pads that can be used in the home. Increasing the exposure of the neonate to phototherapy by using standard phototherapy above and a fiber-optic pad below is more effective than either modality alone. Clinical trials have demonstrated the efficacy of a single intramuscular dose of Sn-mesoporphyrin in managing and preventing neonatal hyperbilirubinemia. Sn-mesoporphyrin, a metalloporphyrin, blocks heme oxygenase, the first step in the production of bilirubin. Sn-mesoporphyrin may be especially helpful in situations in which blood transfusions are prohibited by parents or caregivers for religious reasons or known hemolytic disease puts the neonate at risk for kernicterus.

The preterm or ill neonate or the neonate with hemolysis may be at increased risk from elevated bilirubin levels. Exchange transfusion may be indicated in addition to phototherapy and hydration. The preterm neonate should receive exchange transfusions when the numeric value of the bilirubin measured in milligrams per deciliter reaches the newborn's weight (eg, 11 mg/dL for a newborn weighing 1,100 g [2 lb, 7 oz]). In babies with hemolysis resulting from blood group or Rh incompatibility, reducing hemolysis through the use of intravenous immunoglobulin may obviate the need for exchange transfusion.

Diet and nutrition can be integral to supporting a neonate with conjugated hyperbilirubinemia. Formulas that fortify with medium-chain triglycerides (eg, Neocate, Pregestimil, Similac Alimentum) allow for fat absorption independent of bile acids. Supplementation with fat-soluble vitamins A, D, E, and K is essential. 25-hydroxy (25-OH) vitamin D levels and prothrombin time are easy to assess and can act as a surrogate marker for the others. If galactosemia is suspected, a switch to soy formula is necessary pending results of the newborn screening.

Medications play a limited role in the management of jaundice. Phenobarbital may speed hepatic excretion of bilirubin, even in cases of hemolytic anemia. This drug is also useful in the management of jaundice caused by certain genetic conditions, such as Crigler-Najjar

syndrome. Appropriate antibiotics should be used to combat infections associated with jaundice (eg, cholangitis). For relief of pruritus, ursodeoxycholic acid (15–30 mg/kg/day), hydroxyzine, and rifampin are effective.

Infants with BA require surgery to reestablish bile flow from the liver to the intestinal tract, allowing for passage of bilirubin directly into the lumen of the small intestine (ie, portoenterostomy). Adolescents with gallbladder disease may also require surgical intervention (ie, cholecystectomy).

Prognosis

Most newborns and infants with elevated bilirubin levels have physiologic, breastfeeding, or breast milk jaundice. Prognosis is excellent in these conditions and usually does not require significant intervention. Recently, concern has arisen about a recrudescence of kernicterus, including cases in breastfed, healthy term neonates and infants. Early discharge from the nursery and late follow-up may have contributed to this debilitating complication. Physicians should pursue an appropriate assessment of hyperbilirubinemia in jaundiced newborns and infants and not simply ascribe the symptoms to breastfeeding. Other conditions may require further medical or surgical intervention. Children with metabolic abnormalities require lifelong therapies. Those with hepatic disease may succumb to their hepatic dysfunction or require a liver transplantation. Newborns and infants who undergo surgical correction of BA before 6 weeks of age have a better prognosis than those who undergo surgery after age 6 weeks. These children should be monitored for recurrent episodes of cholangitis, which promotes cirrhosis and the eventual need for liver transplantation.

Older infants, children, and adolescents who develop jaundice often have self-limited conditions that spontaneously resolve, most commonly viral syndromes that affect the liver (eg, Epstein-Barr virus, hepatitis A).

CASE RESOLUTION

Fractionation of the bilirubin revealed 7 mg/dL of conjugated and 3 mg/dL of unconjugated bilirubin; hemoglobin, peripheral blood smear, and haptoglobin were all normal, as was a neonatal genetic screen. Ultrasonography was positive for the triangular cord sign and could not detect a gallbladder. Nuclear scintigraphy showed decreased activity in the intestine, and liver biopsy showed bile duct hyperplasia and an inflammatory infiltrate. Biliary atresia was strongly suspected, and open cholangiography confirmed the condition; portoenterostomy was performed. The infant was started on fat-soluble vitamins (ie, A, D, E, K) and antibiotics for cholangitis prophylaxis.

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CHAPTER 127

Viral Hepatitis

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CASE STUDY

A 15-year-old boy is brought to the office with a 1-week history of intermittent fever, vomiting, diarrhea, and diffuse abdominal pain. His mother reports the appearance of "yellow eyes and skin" on the day before the visit. Her son was previously in good health, and he has not seen a physician in several years. He is taking no medications and has no known ill contacts. He has no history of recent travel outside the United States and denies any unusual food ingestions. His mother reports that he frequently eats at a local fast-food restaurant with his soccer team, but his family does not eat there. He has 1 ear piercing and denies sexual activity, drug use, or tattoos.

The physical examination reveals a temperature of 38.6°C (101.4°F), pulse of 100 beats per minute, and blood pressure of 110/63 mm Hg. The teenager is a well-developed, well-nourished male with yellow skin and sclera. The abdomen is soft, with mild diffuse tenderness, most notably over the right upper quadrant, and normal bowel sounds. The liver edge is palpated 5 cm (2 in) below the right costal margin, and no splenomegaly is present. The rectal examination is normal, with negative fecal occult blood test results.

Questions

1. What are the most common causes of viral hepatitis in children and adolescents?
2. What is the appropriate evaluation for children and adolescents with suspected hepatitis?
3. What complications are associated with viral hepatitis?
4. What treatments are currently available for viral hepatitis, and how does treatment differ depending on the specific etiology?

Hepatitis is an inflammation of the liver that can occur as the result of an exposure to a toxin, such as a chemical or drug, or an infectious agent. In the United States, viruses are the most common cause of hepatitis in children and adolescents, including hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). With the advent of routine immunization for pediatric age groups against HAV and HBV, the prevalence of both infections, as well as complications and long-term consequences, have dramatically decreased. All 3 of these unrelated viruses can produce an acute illness characterized by nausea, malaise, abdominal pain, and jaundice. Hepatitis B virus and HCV also can produce chronic infections, which are generally asymptomatic but are associated with an increased risk for chronic liver disease and hepatocellular carcinoma.

Other common viruses that can cause hepatitis in children in the United States are Epstein-Barr virus (EBV), cytomegalovirus (CMV), varicella-zoster virus (VZV), adenovirus, enteroviruses, and human herpesvirus; however, their contribution to the overall morbidity and mortality associated with infectious hepatitis is minimal. Hepatitis D (as coinfection with hepatitis B) and hepatitis E occur more commonly in other parts of the world.

Epidemiology

In 2017, more than 8,000 cases of viral hepatitis were passively reported from the 50 states and the District of Columbia to the Centers for Disease Control and Prevention (CDC). From 2011 to 2017, the number of HAV cases increased, primarily related to large, food-associated outbreaks and person-to-person transmission in communities of homeless individuals. In the past 10 years, the reported number of HBV cases has stayed relatively stable at approximately 3,000 annually. Over the same period, reported HCV cases increased more than 3-fold, with 3,186 new cases reported in 2017. The CDC notes under ascertainment and under-reporting and estimates that 44,300 acute hepatitis C cases occurred in 2017. The rise in HCV cases is related to an increase in injection-drug use, in part due to the opioid epidemic. There has also been an increase in case ascertainment of HCV, although most infections go undetected. Most new cases are reported in young adults, many with a history of drug use. The CDC states that the total number of acute and chronic hepatitis cases caused by these 3 viruses is probably underestimated because of under-recognition and underreporting but likely exceeds 50,000.

Since initiation of universal immunizations, the incidence of HAV and HBV infections in children and teenagers has significantly declined in the United States. For HAV, the rate of infections has declined from 12 per 100,000 in 1995 (before vaccinations) to a nadir of 0.4 per 100,000 in 2011, where it has remained, other than during outbreaks. Certain situations are associated with increased risk of HAV infection, including crowded living conditions, chronic care facilities, homelessness, military institutions, prisons, child care centers, traveling to endemic areas, outbreak exposure, use of illicit drugs, and high-risk sexual practices (eg, commercial sex workers, men who have sex with men). Poor personal hygiene and inadequate sanitation are also risk factors. In approximately 50% of

HAV cases, however, the source of infection is unknown. Hepatitis A is found worldwide, but specific locations have an increased incidence of infections, including Central and South America, Africa, the Mediterranean region, and Asia.

For HBV, groups at increased risk of infection include individuals who use illicit parenteral drugs, commercial sex workers, men who have sex with men or who have multiple sexual partners, health care workers, neonates born to infected mothers, recipients of hemodialysis, household contacts of carriers of HBV, and immigrants from HBV-endemic areas. Individuals who live in crowded environments with poor hygienic standards, such as institutions for the developmentally disabled or correctional facilities, are also at risk for HBV infection. However, no risk factors are identified in 40% of cases. Worldwide, approximately 5% of the population (ie, 350 million people) is chronically infected with HBV. Individuals with chronic hepatitis B are the primary reservoirs for infection. Areas with the highest incidence of hepatitis B include Southeast Asia, China, the Pacific Islands, most of Africa, and parts of the Middle East.

Approximately 10% to 15% of primary infections with HBV result in a chronic carrier state. The younger children are when they are infected with HBV, the more likely they are to become chronic carriers. Without preventive measures, 70% to 90% of neonates born to infected mothers become carriers, and at least 50% of children infected before the age of 5 years become carriers. Boys have a greater risk of becoming chronic carriers than girls, although the reason for this disparity is not known.

Hepatitis C virus accounts for 20% to 40% of all viral hepatitis in adults. The prevalence in the pediatric age group is estimated to be 0.1%. Individuals at high risk for HCV infection are those who use intravenous (IV) drugs, recipients of transfusions of blood or blood products (especially before 1992), recipients of organ or tissue transplants, health care workers with blood exposure, hemodialysis patients, and, infrequently, sexual or household contacts of infected persons. No identifiable source can be found in at least 35% of cases. In the pediatric population, dialysis patients, institutionalized children, and high-risk newborns (ie, maternal history of IV drug abuse, sexually transmitted infections [STIs], HIV coinfection) are more at risk.

Because hepatitis D only occurs as a coinfection with HBV, high-risk groups are the same, with the exception of health care workers and men who have sex with men. High prevalence rates occur in Eastern Europe, Central Africa, southern Italy, and the Middle East.

Hepatitis E virus (HEV) infection is endemic in low-income countries such as Mexico, Central and Southeast Asia, North Africa, China, and India. No cases of HEV infection acquired in the United States have been reported. In endemic regions, HEV is the most common cause of symptomatic hepatitis in children. Young and middle-aged adults are most commonly affected, and HEV infection is especially severe for pregnant women.

Clinical Presentation

Children with acute hepatitis generally present with symptoms suggestive of a flu-like illness, including fever, malaise, decreased appetite, nausea, and vomiting. They may also report diffuse abdominal pain. Unlike adults, in whom jaundice is a common finding, pediatric patients, particularly infants and young children, are frequently anicteric. Hepatomegaly is often found on physical examination, although not universally, and there may be varying degrees of right upper quadrant discomfort (Box 127.1). A nonspecific macular rash, papulovesicular acrodermatitis (Gianotti-Crosti syndrome), and arthralgia can also occur in the course of HBV infection.

Pathophysiology

Hepatitis A

Hepatitis A virus is a picornavirus composed of single-stranded RNA with only 1 serotype. The most common modes of transmission are through close personal contact and contaminated food and water. This generally occurs by fecal contamination and oral ingestion. Shellfish, such as raw oysters, clams, and mussels, are a frequent source of infection. Infected food handlers may also transmit the disease. With universal immunization of children, most cases now occur in adults 20 years and older.

The average incubation period for hepatitis A is 28 to 30 days (range: 15–50 days). Peak viral secretion occurs before the onset of jaundice. The virus is shed in the stool 2 to 3 weeks before the onset of jaundice and up to 1 week after its appearance. However, most young children with HAV infection are anicteric, so infections often go unnoticed during this highly contagious period (Figure 127.1). The duration of illness is usually 2 to 4 weeks. A prolonged course or relapse occurs in 10% to 20% of adult cases. A chronic carrier state for HAV does not exist, although fulminant infections can occur. Lifelong immunity is conferred after a single infection. Mortality is rare, especially in children.

Hepatitis B

Hepatitis B virus is a double-stranded DNA virus in the *Hepadnaviridae* family. The disease is usually spread by contact with infected blood or blood products, but it can also occur through close interpersonal contact. Although hepatitis B surface antigen (HBsAg) is found in numerous body secretions (eg, blood and blood products, feces, urine, tears, saliva, semen, human milk, vaginal secretions, cerebrospinal fluid, synovial fluid), only serum, semen, vaginal secretions, and saliva have been proven contagious. No fecal-oral transmission occurs. Transmission

Box 127.1. Diagnosis of Hepatitis in the Pediatric Patient

- Diffuse abdominal pain
- Nonspecific symptoms (eg, fever, malaise, anorexia, nausea, vomiting)
- Jaundice (not necessarily in all cases, especially infants and young children)
- Dark urine and light-colored stool
- Pain or tenderness over the liver area
- Hepatomegaly

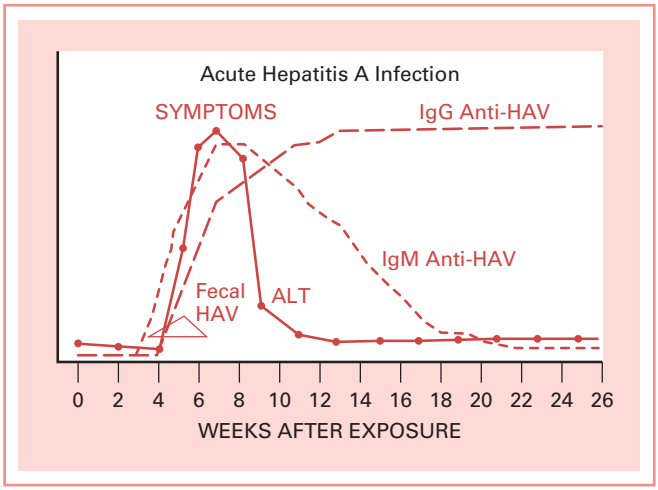

Figure 127.1. Course of acute hepatitis A infection.
Abbreviations: ALT, alanine aminotransferase; HAV, hepatitis A virus; Ig, immunoglobulin.
Reproduced with permission from Tabor E. Etiology, diagnosis and treatment of viral hepatitis in children. In: Aronoff SC, Hughes WT, Kohl S, Speck WT, Wald ER, eds. *Advances in Pediatric Infectious Diseases.* Chicago, IL: Year Book Medical Publishers; 1988.

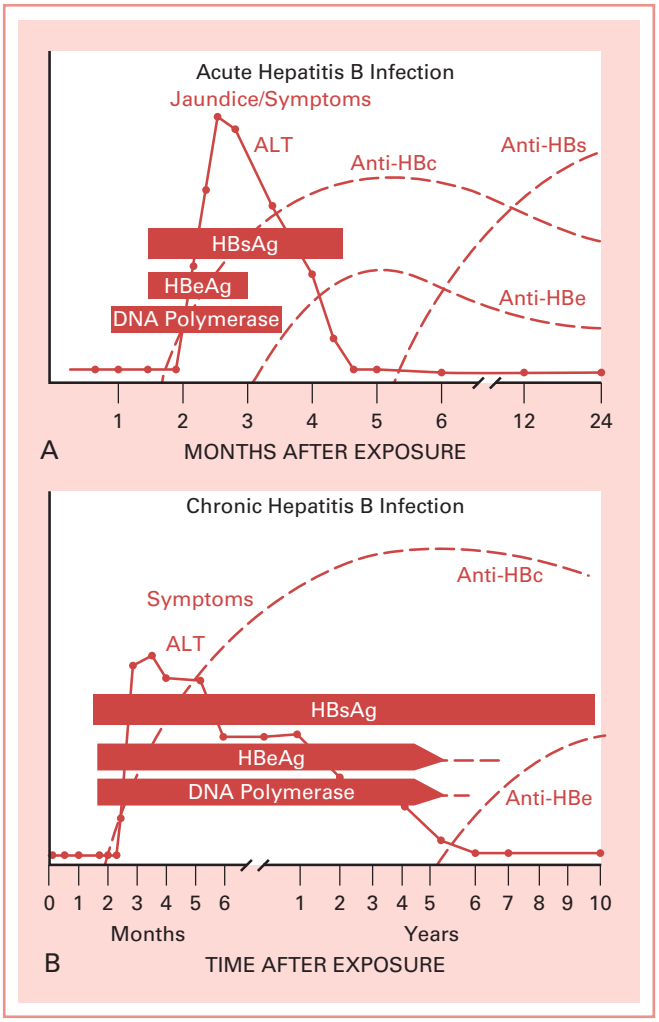

Figure 127.2. Course of hepatitis B infection. A, Acute hepatitis B infection. B, Chronic hepatitis B infection.
Abbreviations: ALT, alanine aminotransferase; HBc, hepatitis B core; HBe, hepatitis B e; HBeAg, hepatitis B e antigen; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.
Reproduced with permission from Tabor E. Etiology, diagnosis and treatment of viral hepatitis in children. In: Aronoff SC, Hughes WT, Kohl S, Speck WT, Wald ER, eds. *Advances in Pediatric Infectious Diseases.* Chicago, IL: Year Book Medical Publishers; 1988.

is facilitated through percutaneous inoculation (eg, tattooing, IV drug use) and exposure of cuts in the skin and mucous membranes to HBV-infected fluids on objects such as razors. Sexual transmission occurs via semen, vaginal secretions, and saliva. Perinatal vertical transmission occurs in neonates whose mothers are acutely infected or chronic carriers and usually occurs from blood exposure perinatally. Postnatal infection from household exposure has been reported, although the exact mode of transmission is unclear. Hepatitis B virus can survive in the environment for longer than 7 days but can be inactivated with household disinfectants, such as bleach diluted 1:10 with water.

The average incubation period for HBV infection is 2 months (range: 1–6 months). Figure 127.2 depicts the typical course of acute hepatitis B infection, along with the course of the chronic carrier state.

Hepatitis C

Hepatitis C virus is a single-stranded RNA virus in the *Flavivirus* family; it is able to mutate rapidly, thus escaping detection by the host's immune system. Like HBV, HCV can be spread through contact with contaminated blood and blood products. Previously, children with frequent exposure to blood products had increased risk, but currently the risk of HCV infection after transfusion is less than 1 per 2 million units of blood transfused. Most acute cases reported to public health occur in individuals who use drugs who have shared needles or paraphernalia. About one-third of young adult (aged 18–30 years) individuals who engage in injection drug use in the United States have HCV infection. For children, maternal-fetal transmission is the most common route of infection, and the rate of vertical transmission is about 5% to 6%. Transmission of infection via household and sexual contact has been demonstrated but is uncommon.

The incubation period is variable, ranging from 2 weeks to 6 months, and averages 6 to 7 weeks. Most affected children are anicteric and asymptomatic. If symptomatic infection is present, it is usually mild, insidious, and indistinguishable from infections caused by HAV or HBV. Jaundice occurs in approximately 25% of patients. Fulminant hepatitis is extremely uncommon.

Hepatitis D

Acute hepatitis D infection is caused by a distinct single-stranded RNA virus that requires HBsAg for replication. The virus and a delta antigen are enclosed in an envelope of HBsAg. Transmission is similar to HBV, but vertical transmission is uncommon. Hepatitis D infection occurs as a coinfection with HBV or a superinfection in a chronic carrier of HBV. Acute disease is usually more severe and carries a higher risk of fulminant hepatitis than HBV infection alone.

Hepatitis E

Hepatitis E virus is caused by an enterically transmitted RNA virus. There are 7 genotypes in its genus, *Orthohepevirus*, and the viruses can infect humans and multiple animal species. Transmission is primarily through contaminated drinking water and fecal-oral spread, especially during rainy or monsoon seasons in endemic areas. Hepatitis E virus is the most common viral hepatitis worldwide, and sporadic infection is common in Africa and the Indian subcontinent. Nearly all HEV infections in the United States have been reported in travelers returning from endemic areas.

The incubation period ranges from 2 to 6 weeks, with most cases of acute infection being self-limited. Mortality is low in endemic populations, except in pregnant women. Mother-to-neonate transmission is common and contributes to fetal loss and perinatal mortality. Hepatitis E virus can cause chronic infection, but this usually occurs in individuals who are severely immunocompromised.

Differential Diagnosis

The differential diagnosis of hepatitis depends on the patient's demographics (eg, age), possible exposures, and immunization history. Possible infectious causes in neonates include overwhelming bacterial sepsis, VZV, and congenital infections (TORCHES [toxoplasmosis, other agents (syphilis, hepatitis B, varicellazoster virus [VZV], human immunodeficiency virus [HIV], parvovirus B19, enteroviruses, lymphocytic choriomeningitic virus), rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV)]), in addition to HBV infection. Perinatal transmission of HAV is rare. Genetic disorders and anatomical abnormalities causing biliary obstruction (eg, biliary atresia) should also be considered (see Chapter 126).

In older infants and children, in addition to HAV, HBV, and HCV, other viral etiologies include EBV, CMV, enteroviruses (including coxsackieviruses), adenovirus, VZV, human herpesvirus, and, uncommonly, rubella, rubeola, and HIV. In the United States, bacterial, parasitic, and fungal causes of liver infections are uncommon. Bacterial processes include pyogenic abscesses and sepsis. Parasitic agents include *Plasmodium* species (causes of malaria), *Trypanosoma cruzi,* and amoebic abscesses, among others, and these should be considered in individuals from endemic areas and returning travelers. Acute or chronic anemias, such as sickle cell disease, can also cause hepatomegaly and jaundice. Noninfectious conditions to consider include drug-induced hepatitis (eg, prescribed medications such as isoniazid or phenytoin and illicit drugs), toxin ingestion (eg, acetaminophen, herbal remedies), and conditions such as cystic fibrosis, α_1-antitrypsin deficiency, Wilson disease, and other congenital disorders such as Caroli disease (dilatation of the intrahepatic bile ducts).

In adolescents, viral etiologies to consider are similar to those listed for children. Other infectious processes to consider in the adolescent age group include biliary tract infections, bacterial sepsis, and Fitz-Hugh–Curtis syndrome (ie, liver inflammation associated with pelvic infections, especially with *Chlamydia trachomatis* or *Neisseria gonorrhoeae*). The list of prescribed and illicit drugs that may cause liver toxicity is extensive and includes oral contraceptives, seizure medications, alcohol, inhalants, acetaminophen, and tetracycline.

Evaluation

History

A comprehensive history should be obtained in children of all ages (Box 127.2). A dietary and travel history is essential, especially when considering HAV and HEV infection.

For neonates and young infants, a complete maternal and obstetric history should be obtained and include the following questions: Does the mother have any history of IV drug use? Does the mother come from an area in which hepatitis is endemic, such as Southeast Asia? Did the mother receive prenatal care? Was hepatitis B screening performed prenatally or at delivery? Did the mother have any known STIs or sexual contacts with hepatitis B-infected individuals?

History in adolescents should also include queries about sexual activity, history or symptoms of STIs, the number of sexual partners, parenteral drug use, and tattoos.

Physical Examination

Most children with viral hepatitis are asymptomatic and generally do not present for medical evaluation. For symptomatic children, there are no clues on the examination to aid in differentiating the causes. However, a complete physical examination should be performed to help rule out other etiologies. All vital signs should be recorded, including temperature to monitor for fever. In children who are vomiting, signs of dehydration (eg, tachycardia, evidence of orthostatic hypotension, dry mucous membranes, tenting of the skin, sunken eyes, lethargy) should be noted. Growth parameters,

Box 127.2. What to Ask

Hepatitis

- Does the child have any history of fever, malaise, anorexia, or weight loss?
- Has the child experienced any vomiting or diarrhea?
- Is any abdominal pain or discomfort present? If so, in what location?
- Are yellow eyes or any changes in skin color apparent? If so, for how long?
- Is the color of the urine dark and the stool light?
- What is the child's recent travel history?
- Has the child ingested any shellfish in the previous 1 to 2 months?
- Has the child been in contact with any individuals with hepatitis or jaundice (including sexual contacts)?
- Is the child taking any medications (eg, isoniazid)?
- Does the child have a history of transfusion with blood or blood products?
- Is the adolescent sexually active, or has the adolescent had any known exposure to sexually transmitted infections (STIs)?
- Does the adolescent have a history of intravenous (IV) drug use or tattoos?
- Does the mother have a history of hepatitis, IV drug use, STIs, or multiple sexual partners?

particularly weight, should be obtained and compared with previous measurements, if available.

The skin should be examined for jaundice; evidence of pruritus (eg, excoriations), which may be associated with elevated bilirubin; or a nonspecific rash. Icterus of the sclera, tympanic membranes, and palate should also be noted. The abdomen should be palpated for tenderness and organomegaly, particularly hepatomegaly. The liver span should also be determined by percussion because it will help monitor the patient's progress. Splenomegaly, which is not typically found in hepatitis, indicates a different diagnosis, such as leukemia, or another infectious cause, such as EBV or CMV. A rectal examination should be performed to look for masses or blood in the stool, which may suggest a neoplastic etiology.

A neurologic examination is important to document any signs of encephalopathy from hyperammonemia, which occurs more commonly in chronic liver disease or fulminant hepatic failure.

Laboratory Tests

The initial laboratory tests needed are directed by the severity of illness in the child at presentation. At a minimum, these include liver function tests (LFTs), including alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and total and direct bilirubin, and coagulation studies (ie, prothrombin time and partial thromboplastin time). Monitoring prothrombin time is particularly useful because of its rapid turnaround time and predictive utility; if the value is greater than 3 seconds above the upper reference range limit (international normalized ratio ≥1.5), prognosis is poor.

Serologic antibody testing for hepatitis A (HAV-immunoglobulin [Ig]M and HAV-IgG) and hepatitis B (HBsAg, anti-HBs, hepatitis B e antigen [HBeAg], anti-HBe, and hepatitis B core antibody) should also be performed. Nucleic acid amplification testing (NAAT), polymerase chain reaction, and hybridization assays to detect and quantify hepatitis B DNA in plasma and serum are also available. Diagnostic antibody patterns for HAV and HBV are shown in Figures 127.1 and 127.2. For HAV, positive HAV-IgM results are suggestive of acute infection, and positive HAV-IgG results may be seen after vaccination or prior to infection. Hepatitis B virus vaccine contains surface antigen, so only anti-HBs will be seen postvaccination. Of note, HBsAg may be detected for fewer than 3 weeks after vaccination.

Serum antibody to HCV (anti-HCV) should be sent, especially for individuals with risk factors for infection and if test results are negative for HAV and HBV. The current third-generation antibody testing has 97% sensitivity and 99% specificity, making results more reliable than previously available immunoassays. Within 3 to 6 weeks of onset of hepatitis, approximately 80% of individuals will have positive anti-HCV antibody test results. Hepatitis C virus NAAT can detect HCV RNA in serum before seroconversion. Nucleic acid amplification testing has generally replaced the immunoblot for confirmatory testing and can also be used in other situations (eg, an immunocompromised individual who may not make antibodies, in infants younger than 18 months who may have circulating maternal antibodies).

Serologic markers for hepatitis D (IgM and IgG anti-hepatitis D virus [anti-HDV]) can be sent when concurrent HBV infection is evident. Immunoglobulin M anti-HDV may be seen with acute or chronic infection. Hepatitis D virus RNA testing is available and should be performed if chronic HBV infection with superinfection with HDV is suspected.

Other serologic testing may be performed as indicated by history and physical examination, as discussed previously. A complete blood cell count and comprehensive metabolic panel may be needed in ill-appearing children, especially with signs of dehydration. A urinalysis for bilirubin should be done. In severe or complicated cases of viral hepatitis, additional testing, such as liver biopsy or ultrasonography, may be indicated. For these cases, consultations with specialists in infectious diseases and hepatology are needed.

Management

Most cases of acute HAV and HBV infections are uncomplicated, and therapy consists of supportive care. These illnesses are usually self-limited, and no specific therapy is available. Adequate nutrition and hydration are of primary importance. Therefore, the intake of sufficient calories and fluids should be ensured. A low-protein diet during the acute phase of the illness may be considered. The use of antipyretics such as acetaminophen or ibuprofen for fever usually does not pose a problem in patients with mild disease and acutely elevated LFTs. However, because it is metabolized by the liver, it is preferable to limit the use of acetaminophen. Physical activity should be limited until patients feel better and LFTs return to reference range. Children and adolescents can return to school when they are no longer jaundiced; they may also resume a typical diet at that time.

In children with more severe symptoms, IV hydration and an antiemetic may be indicated. Hospitalization is required for children who are moderately to severely dehydrated, are unable to tolerate fluids, or have evidence of fulminant liver failure. Treatment is aimed at correcting any metabolic abnormalities or electrolyte disturbances, including hypoglycemia. It may be necessary to correct coagulopathies with vitamin K, fresh frozen plasma, and cryoprecipitate. Total parenteral nutrition may be required to maintain caloric needs.

Consultation with a pediatric gastroenterologist is important for management of acute fulminant liver failure or chronic, active hepatitis in children. No specific treatments are available for fulminant acute HAV infection. However, a few treatment options are available for children with chronic infection with HBV and HCV. Treatment options for both infections include immunomodulators such as interferon-alfa, available as interferon alfa-2b and pegylated recombinant interferon alfa-2a. For HBV infection, 5 antiviral agents are available, including entecavir, lamivudine, telbivudine (nucleoside analogues), and tenofovir and adefovir (nucleotide analogues). For HCV infection, direct-acting anti-HCV medications are approved and are the standard of care for adults but not yet for children. Enrollment in a clinical trial should be considered for children with HCV infection. Information is available at www.hcvguidelines.org.

Children and adolescents with chronic HBV and HCV infection and their parents or guardians should be counseled to avoid hepatotoxic medications and alcohol. Parents or guardians should be informed of the possibility of transmission to others, and patients

should refrain from donating blood, organs, tissue, or semen. In addition, sexually active adolescents should be informed of the possible risk to sexual partners. Toothbrushes and razors should not be shared among household contacts. Most children with chronic HBV and HCV infection should not be excluded from child care centers because of their infection. Possible reasons for exclusion of children with HBV infection include biting behaviors, bleeding disorders, and generalized dermatitis. Because children with chronic HBV and HCV infection are at risk for the development of serious liver disease, they should be followed regularly by their primary care physician in conjunction with a pediatric gastroenterologist.

Prevention

All children should routinely receive immunizations for HBV (starting at birth) and HAV (starting at 12 months of age). For older children and adolescents, review of their immunization records should be performed, and catch-up doses of hepatitis A and B vaccine should be provided as needed. In the United States, 43 states and the District of Columbia require proof of hepatitis B vaccination for school enrollment.

Hepatitis A

Routine immunization for children starting at the age of 12 months has been recommended since late 2006. In 1995, target groups were given hepatitis A vaccine, which led to a more than 85% decline in disease incidence. Handwashing by food handlers, medical personnel, and child care workers is among the primary methods of preventing the spread of HAV. Contact precautions should be used for hospitalized patients for at least 1 week after onset of symptoms. Active immunization with HAV vaccine or passive immunization with immune globulin intramuscular (IGIM) is recommended as postexposure prophylaxis for all people who have had intimate exposure to infected individuals. Hepatitis A virus vaccine and IGIM may be administered at the same time in different sites. Postexposure IGIM is generally not indicated for contacts at school or work, but it is indicated for HAV-exposed infants younger than 12 months, because they are not candidates for vaccination. The dose of IGIM is 0.02 mL/kg within 48 hours of exposure but no later than 2 weeks after exposure. Immune globulin intramuscular is 80% to 90% effective in prevention of clinical HAV disease. Hepatitis A virus vaccine may be used for postexposure prophylaxis for most healthy individuals aged 1 to 40 years.

Pre-exposure prophylaxis with HAV vaccine is preferred for individuals who are eligible for vaccination. Infants younger than 12 months and individuals with contraindications are not vaccine candidates. Hepatitis A virus vaccine should be administered 2 weeks before expected exposure (eg, travel to endemic areas). Two inactivated HAV vaccines are licensed in the United States in pediatric formulation for children 12 months and older. Formulations for adults aged 19 years and older are also licensed. The vaccine efficacy is greater than 94% for preventing clinical HAV disease. Two doses of the vaccine are recommended and should be given initially and 6 to 12 months later. Combination vaccine against HAV and HBV is licensed for individuals older than 18 years. For IGIM given pre-exposure, the dose is 0.02 mL/kg if the planned stay is less than 3 months and 0.06 mL/kg every 5 months for longer stays.

In addition to routine childhood immunization, specific other groups for whom hepatitis A vaccine is recommended include travelers to endemic areas who are older than 12 months, close contacts of newly arriving international adoptees, individuals with chronic liver disease, men who have sex with men, users of injection and illicit drugs, people with clotting-factor disorders, and those at occupational risk of exposure (eg, food handlers, nonhuman primate handlers, health care workers, child care workers, HAV laboratory researchers).

Hepatitis B

Preventive strategies for hepatitis B include universal immunization of all neonates beginning at birth and catch-up immunizations for unimmunized older children and adolescents, as well as adults with increased risk of HBV. Postexposure prophylaxis with HBV vaccine is recommended to protect unimmunized individuals.

Use of hepatitis B immunoglobulin (HBIG) for postexposure prophylaxis is recommended in specific settings, including infants born to mothers who are known to be HBsAg positive or mothers with unknown status that cannot be determined within 12 hours of birth. Passive immunization with HBIG is also recommended for susceptible individuals with discreet, identifiable percutaneous, mucosal, or sexual exposure to blood or body fluids of a person known to be HBsAg positive or whose status cannot be determined. Simultaneous active immunization with HBV vaccine should also be initiated in these cases. Standard IV immunoglobulin does not contain sufficient antibodies to HBV and should not be used for prophylaxis.

Hepatitis B virus vaccine is recommended for all newborns, infants, children, and adolescents through age 18 years (see Chapter 37). The vaccines are produced using recombinant DNA technology and contain only HBsAg. In the United States, HBV vaccines are available as single component and combination formulations. They are generally well tolerated and provide long-term protection for immunocompetent recipients. Newborns should receive the first dose before discharge from the nursery, the second dose 1 to 2 months later, and the third dose at 6 to 18 months of age. Infants should not receive the third dose before 6 months of age. Dosing intervals for other individuals are similar, and for adolescents (11–15 years of age), a 2-dose regimen using hepatitis B vaccines (eg, Recombivax HB, Engerix-B) is approved by the US Food and Drug Administration. The CDC also recommends a 3-dose HBV vaccine series for adults who are at high risk of infection and those desiring protection against HBV.

Perinatal vertical transmission of HBV can be prevented by giving newborns HBIG (0.5 mL intramuscularly) within 12 hours after birth and HBV vaccine concurrently (at a different site). This practice prevents approximately 90% of chronic infections in neonates born

to mothers who are HBsAg and HBeAg positive. Postimmunization serologic screening is recommended for these infants at 9 to 12 months of age because approximately 5% of infants become carriers despite appropriate preventive vaccination. Special schedules for active and passive immunizations against HBV should be consulted for preterm neonates who weigh less than 2,000 g (4 lb, 6.5 oz) (see Chapter 37).

Hepatitis C

No vaccine exists for the prevention of HCV infection. Because IV immunoglobulin is manufactured from plasma that is HCV-antibody negative, it is not recommended for prophylaxis.

Current recommendations include screening individuals with risk factors of HCV infection (see the Pathophysiology section), including children born to women who are infected with HCV; people born between 1945 and 1965; individuals who use injection or illicit drugs; recipients of immunoglobulin between April 1993 and February 1994, blood transfusions or solid organ transplants before July 1992, or clotting factors before 1987; hemodialysis patients; patients with known exposure to HCV; patients who have HIV infection; incarcerated individuals; and individuals with clinical hepatitis found not to have hepatitis A or B.

Hepatitis D

Prevention of HBV infection through universal vaccination is the most important means of controlling HDV infection.

Hepatitis E

Availability of safe, clean drinking water is the most effective means of preventing HEV infections and their spread. No HEV vaccine is available in the United States, but a recombinant vaccine has been approved in China.

Prognosis

The prognosis for children with viral hepatitis depends on etiology, as well as the child's age and underlying health status. For HAV infection, the outcome is generally good, with an uneventful recovery for healthy children. Infants and children infected with HBV are at high risk of becoming chronic carriers, especially if infected at a young age. Approximately 25% of carriers develop chronic, active hepatitis, which often progresses to cirrhosis. In addition, the risk of developing hepatocellular carcinoma is 12 to 300 times higher in these patients compared with the general population.

Chronic hepatitis also occurs with HCV infection in 75% to 85% of adults, but it appears to occur less commonly in children. Autoimmune complications such as arthritis, serum sickness, and erythema multiforme are common with chronic disease. About 10% to 20% progress to cirrhosis and hepatic failure, and HCV infection is among the leading indications for liver transplant for adults in the United States. Hepatocellular carcinoma has also been described in a small proportion of patients.

Complications of hepatitis D, such as cirrhosis and portal hypertension, are not uncommon. They occur more frequently with HBV infection associated with HDV infection than with HBV infection alone and progress more rapidly. Infection with HEV infrequently results in chronic infection but is more likely to occur in individuals who are severely immunocompromised.

Fatal hepatitis A infection is a rare occurrence. The overall mortality associated with HBV, HCV, and HEV infections is also low (approximately 1%–2%), although HEV infection can be fatal in 20% of infected pregnant women. Mortality rate may increase to 30% for HBV infection with HDV coinfection.

CASE RESOLUTION

The teenager has a classic presentation of viral hepatitis despite no clear history of exposure, such as travel to an endemic area. Statistics point to probable infection with hepatitis A, and exposure possibly occurred at the fast-food restaurant. Because he does not appear to be dehydrated or seriously ill, he can be managed as an outpatient. Serologic testing for hepatitis A, B, and C should be performed, in addition to LFTs and coagulation tests. The parents should be informed of the probable diagnosis, and, if confirmed as hepatitis A infection, all household contacts should receive hepatitis A vaccine or prophylaxis with immunoglobulin. They should also be educated on the infectivity of the disease and counseled about supportive therapy. Public health officials should be consulted for management of other cases of individuals who were possibly exposed. The boy should have limited physical activity while symptomatic and should be scheduled for a follow-up visit in a few days for repeat LFTs and coagulation tests. The prognosis is good.

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PART 12

Neuropsychiatric Disorders

CHAPTER 128

Hypotonia

Hanalise V. Huff, MD, MPH, and Kenneth R. Huff, MD

CASE STUDY

A 6-month-old girl is brought to the office because she no longer reaches for her toys. The pregnancy was full term, but the mother remembers that the fetal kicking was less than with an older brother. Delivery was uncomplicated, and the newborn fed well from birth. The girl began to show visual attention at 2 to 3 weeks, smiled socially at 1 month, and pushed up while prone at 2 months. Although she turned over at 4 months, she has not done this in the past month. She no longer reaches up to the mobile over her crib.

On physical examination, the girl lies quietly on the table and watches the examiner intently. Her growth parameters, including head circumference, are normal. After she has been undressed, it is apparent that she exhibits "see-saw" breathing (ie, abdomen rises with inspiration) and has a frog-leg posture (ie, batrachian position). The cranial nerve examination is normal except for head-turning strength. When she is pulled to a sitting position, her head lags far behind and her arms are straight at the elbows. She cannot raise her arms off the table. When a rattle is placed in her hands, she manipulates the toy, which she regards from the corner of her eye. Deep tendon reflexes are absent, but her pain sensation is intact.

Questions

1. What is meant by hypotonia?
2. How is the level of nervous system involvement determined in infants with hypotonia?
3. What is the significance of a loss of developmental milestones or abilities?
4. When are diagnostic tests appropriate for a child with hypotonia?
5. How are clinical management issues related to prognosis?

Infants with decreased tone are referred to as hypotonic or "floppy." *Hypotonia* is most simply defined as lower than normal resistance to passive motion across a joint but is also suggested by abnormal posture. Although the lack of resistance may have other components (eg, connective tissue abnormalities suggested by an unusual range of joint mobility and hyperelastic skin, features of Ehlers-Danlos syndrome, features of Down syndrome), muscle strength is a key component. Tone can be used as a surrogate indicator of strength in infants who cannot cooperate with resistance testing. Weakness can also be inferred from functional observations and the inability to sustain limbs against gravity or the lack of a withdrawal response of a limb to a painful stimulus. Identification of the affected central nervous system (CNS) level (eg, upper motor neurons, lower motor neurons, spinal cord, anterior horn cell, peripheral nerve components, myoneural junction, muscle fibers) is most important in determining the etiology of hypotonia in infants and children. Only after this localization is the likely pathology defined in most cases.

Epidemiology

Hypotonia is not unusual in neonates, and non-neuromuscular causes of hypotonia are more common than neuromuscular conditions. Non-neuromuscular causes include hypoxic-ischemic encephalopathy and brain lesions related to preterm birth, such as intraventricular hemorrhage and periventricular leukomalacia. Genetic abnormalities also are frequently present shortly after birth. Spinal muscular atrophy (SMA) is a common progressive genetic condition with a prevalence similar to that of cystic fibrosis (approximately 1 in 5,000). Duchenne muscular dystrophy (DMD), which manifests between ages 2 and 5 years, is the most common neuromuscular condition in childhood, with a prevalence of 1 in 1,700 to 1 in 3,500 male births. The *DMD* gene has been found to spontaneously mutate in approximately 50% of patients. Among non–genetically acquired disorders, the prevalence of acute postinfectious polyneuritis (ie, Guillain-Barré syndrome) is 2 to 8 per 100,000.

Clinical Presentation

Hypotonia in infants often presents with unusual posture, diminished resistance to passive movements of the limbs or trunk, or an excessive range of joint mobility. Infants with hypotonia have delayed motor milestones, decreased movements, and poor head and trunk control (Figure 128.1). Older children may have decreased ability to resist with strength testing of individual muscle groups as well as impaired functional strength in sitting, standing, walking, climbing, or running (Box 128.1). Swayback posture in standing may be indicative of hip girdle or proximal weakness. Pointed toes in the supine position may be indicative of an upper motor cause.

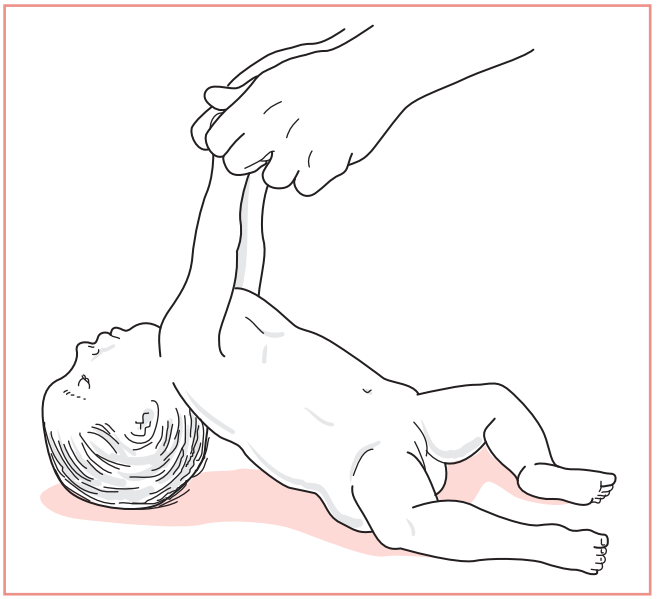

Figure 128.1. Traction maneuver. The arms are completely extended, head control is poor, and the legs are abducted at the hip.

Box 128.1. Diagnosis of Hypotonia in the Pediatric Patient

- Decreased resistance to passive movement of a joint
- Muscular weakness in older children
- Etiologic diagnosis related to the nervous system level of the lesion

Pathophysiology

Tone is a product of connective tissue structural elements, including ligaments, tendons, and joint capsules; muscle fiber number and integrity; and nerve fiber input to muscle. Nerve input to the muscle includes the number and myelination of axon fibers, trophic factors from the nerve, and frequency of action potentials depolarizing the muscle membrane. The control of tone through the anterior horn cells is complex and involves more than just the corticospinal tract (upper motor unit) but also other descending tract influences. Lesions of the neuromuscular apparatus (lower motor unit), which includes muscle, nerve, nerve sheaths, and anterior horn cells, can most directly decrease tone; however, lesions of any of the other structures at many levels of the nervous system also can affect tone. The final common pathway of upper or lower motor unit modification of tone is through the gamma loop, which is part of the fusimotor system. The fusimotor system consists of gamma motor neurons within the anterior horn of the spinal cord innervate the contractile muscle portions on each end of the intrafusal fiber and enhance the sensitivity of the sensory endings to stretch, which in turn transmit signals back to the alpha motoneurons in the anterior horn, thereby innervating the rest of the muscle. Different CNS levels (ie, motor cortex, thalamus, basal ganglia, vestibular nuclei, reticular formation, cerebellum) can modify tone through their effect on the gamma loop motor neuron.

The nature of the lesion at different levels of the nervous system may be quite variable. For example, ultrastructural abnormalities occur in congenital myopathies, including those related to respiratory chain defects; anterior horn cell apoptosis occurs in SMA and may also occur with ischemic insults; stripping of myelin by macrophages occurs with acute postinfectious polyneuritis; and muscle voltage-gated channels are involved in periodic paralyses.

Differential Diagnosis

Distinguishing clinical features in determining the level of the lesion in the nervous system includes pattern of weakness, activity of deep tendon reflexes, presence of fasciculations or sensory loss, cerebrospinal fluid findings, serum muscle enzyme levels, electromyography (EMG) pattern, nerve conduction studies, and histologic appearance or assays of the muscle or nerve biopsy. When assessing the child with hypotonia it is useful to separate first upper motor neuron or brain causes from neuromuscular causes (Table 128.1). The former includes perinatal hypoxia-ischemia, intracranial hemorrhage, and cerebral dysgenesis. These problems may present with hypotonia in infancy but later are evident as a static encephalopathy. A child with a CNS cause may have a below-normal level or range of attention and may lack age-appropriate social skills. Seizures or hemiparesis also signify a likely CNS cause. In an older child, fine motor coordination, quality and repertoire of movements, and language may be affected. The deep tendon reflexes may be brisk or easily elicited. The Babinski reflex may be dorsiflexor. In infants, fisting of the hands, scissoring of the extended legs on vertical suspension, and movement through postural reflexes, such as the asymmetric tonic neck reflex, are clues to an upper motor neuron process. In a patient with an upper motor neuron lesion, serum muscle enzymes, EMG, nerve conduction studies, and muscle biopsy are all normal. However, the child with 1 of the neuromuscular causes for hypotonia, including congenital myopathy, SMA, muscular dystrophy, and acute postinfectious polyneuritis, that does not also involve brain or facial nerves or muscles may have an interested and visually attentive facial appearance. This may be the case even in the presence of severe weakness that allows only sparse or nearly absent limb movements. With many of these neuromuscular lesions, deep tendon reflexes may be difficult to elicit or may be absent.

Older children may display a different pattern of weakness that is suggestive of the level of involvement. If the weakness is preferentially in the upper extremity extensor and lower extremity knee flexor, ankle dorsiflexor, and ankle evertor muscle groups (ie, antigravity muscles), the lesion likely involves the upper motor neuron. Static bilateral hemiparesis is suggestive of severe hypoxemic-ischemic insult, and in the child who was born preterm, diplegia is suggestive of periventricular leukomalacia. A differential weakness in opposing muscle groups resulting from CNS causes may be present and contribute to hypotonia for a long period before spasticity intervenes and increases tone. If the weakness involves agonist and antagonist muscles equally across a limb joint, however, it

Table 128.1. Exemplified Differential Diagnosis of Infantile Hypotonia by Nervous System Level

Level	*Specific Lesion*
Cerebral hemisphere	Static encephalopathy related to perinatal or prenatal insults Dysgenesis (eg, Down syndrome, Prader-Willi syndrome) Degenerative conditions (eg, storage disease)
Spinal cord	Traumatic transection Dysraphism or other malformation Epidural abscess
Anterior horn cell	Spinal muscular atrophy Enterovirus-associated myelitis Arthrogryposis multiplex congenita
Peripheral nerve	Leukodystrophy Hereditary sensorimotor neuropathy type 3 Acute polyneuritis (rarely occurs in infancy)
Myoneural junction	Myasthenia gravis (transient or congenital) Toxin (botulism or aminoglycoside antibiotics) Hypermagnesemia
Muscle	Congenital structural myopathy (ie, nemaline, central core, myotubular, multicore, congenital fiber-type disproportion) Congenital myotonic dystrophy Congenital muscular dystrophy (eg, Fukuyama type, Walker-Warburg syndrome, muscle eye brain disease, merosin-deficient myopathy) Mitochondrial myopathy (cytochrome-*c* oxidase deficiency)
Systemic	Aminoacidopathy and organic acidemia, hypercalcemia, renal tubular acidosis, rickets, celiac disease, hypothyroidism, collagen disease, congenital heart disease, glycogen storage disease (eg, Pompe disease), carnitine deficiency, peroxisomal disorders)

probably represents a neuromuscular process. It is also important to remember that hypotonia can result from disorders with combined lesions in levels above the lower motor neuron and in the motor unit. Examples include Krabbe disease, glycogen storage disease type 2 (ie, Pompe disease), congenital myotonic dystrophy, mitochondrial and peroxisomal disorders, and hypoxic-ischemic insults involving the upper motor neuron and anterior horn cell.

Evaluation

A methodical assessment using clinical and laboratory features in children to localize the lesion to a particular nervous system level can help anatomically narrow a wide differential diagnosis (Table 128.2).

History

Particular aspects of the history are especially important (Box 128.2). Strength of fetal movements relative to other pregnancies and ischemic, toxic, metabolic, or infectious fetal exposures should be ascertained. Relatively decreased fetal movements may signify an early degenerative condition. Polyhydramnios can signal prenatal weakness in swallowing. Birth events should be investigated for sources of possible insults to the neonatal nervous system, such as preterm status or birth asphyxia. The physician should determine whether any of the child's developmental skills have been lost. Any associated loss of tone or strength could signify a progressive condition rather than a static problem, such as would occur with a birth injury. The acuity of the developing

Box 128.2. What to Ask

Hypotonia

- Were the fetal movements of the child abnormal or less than those of previous pregnancies?
- Was the pregnancy full term? Was the delivery complicated?
- Does the mother, do any siblings, or do other family members suffer from a similar weakness?
- Has the child lost any developmental skills? Is the problem getting worse?

Table 128.2. Simplified Approach to Localization of the Lesion for the Diagnosis of Hypotonia

	Anatomic Site				
Clinical Feature	*Cerebrum*	*Spinal Cord*	*Anterior Horn Cell*	*Neuromuscular Junction*	*Muscle*
Alertness	Decreased	Normal	Normal	Normal	Normal
Cry	Decreased	Normal	Normal/weak	Weak	Normal/weak
Eye movements	Sometimes abnormal	Normal	Normal	Abnormal	Normal
Tongue fasciculations	Absent	Absent	Present	Absent	Absent
Muscle bulk	Normal	Normal	Decreased	Normal	Decreased
Deep tendon reflexes	Normal/increased	Decreased/increased	Absent	Normal	Normal/decreased

weakness is another important clue in the differential diagnosis. Rapid-onset hypotonia accompanied by constipation, poor feeding, and other bulbar involvement may be suggestive of botulism. Acute losses of tone and strength may also occur with enteroviral poliomyelitis, Guillain-Barré syndrome, myasthenia, and myositis. Relapsing-remitting courses of hypotonia may occur with myasthenia; metabolic myopathies, including mitochondrial disorders; and periodic paralysis in the older child. The child who has recently been hiking should be evaluated for tick paralysis. A parallel deterioration in intellectual functions or seizures may be indicative of leukodystrophy, storage disorder, or another degenerative disorder, including 1 of the several types of Leigh disease, particularly if ataxia, brain stem symptoms, and respiratory dysfunction subsequently occur.

Family history should be determined as well. The presence of weakness or hypotonia in other family members or prior unexplained neonatal or childhood deaths in the family may indicate a genetic or maternal basis for the patient's hypotonia.

Physical Examination

Dysmorphic features should be noted in children with developmental delay who exhibit hypotonia, because these features may be suggestive of cerebral dysgenesis as part of a multiple malformation syndrome or a chromosomal anomaly (eg, the characteristic stigmata of Down syndrome) or as part of a neuromuscular condition (eg, narrow face, hypoplastic mandible, high-arched palate, thin ribs with deformed rib cage, pectus excavatum). In the older child, characteristics of dermatomyositis, such as a rash on the hands and coloration of the eyelids, may be noted.

Poor feeding with small male genitalia in the neonate may be suggestive of Prader-Willi syndrome. A large tongue with decreased growth parameters may be indicative of hypothyroidism. Hepatomegaly may occur with Niemann disease and cerebrohepatorenal (ie, Zellweger) syndrome. Signs of brain dysfunction, such as lethargy, unresponsiveness to the environment, and lack of social skills, should be noted. Acute signs of sepsis along with generalized hypotonia in a neonate may be indicative of an inborn error of metabolism; these are signs of decompensation, and emergent intervention is required. Age-appropriate cognitive abilities should be assessed as a measure of cerebral function. This assessment may range from primarily observation of visual attention (eg, loss of visual following without loss of oculocephalic reflex) in the very young infant to evaluation of language and academic skills in the older child. Cranial nerve examination to assess eye movements, facial strength, and presence of tongue fasciculations is important, especially in the differential diagnosis of many neuromuscular conditions. Ocular muscle involvement may be part of mitochondrial myopathies, myotubular myopathy, and myotonic dystrophy. Blindness and hyperacusis responses may be suggestive of Tay-Sachs disease. Deafness may be part of a mitochondrial disorder. Facial muscle involvement is common in some congenital and mitochondrial myopathies and myotonic dystrophy but is not a part of SMA. Sucking and swallowing difficulty is a feature of SMA, congenital myotonic dystrophy, myotubular and nemaline myopathies, neonatal myasthenia, and Prader-Willi syndrome, in addition to birth asphyxia.

The degree of hypotonia and strength in the trunk and limbs should be examined carefully in the awake infant with the head in midline. Passive pronation, supination, flexion, extension, and gentle shaking of hands and feet may be signs of hypotonia. Additional maneuvers to assess hypotonia (Box 128.3) include the traction maneuver to assess head control (ie, neck tone; Figure 128.1), horizontal prone suspension to assess the trunk (Figure 128.2), the scarf sign and axillary suspension to assess the shoulder girdle (Figure 128.3 and Figure 128.4), and the popliteal angle to assess extremity tone (Figure 128.5). Preterm neonates normally exhibit a caudal-rostral progression of tone development, particularly flexor tone, correlated with age up to 40 weeks' term.

Individual joint movements should be observed, and agonist-antagonist strengths should be tested bilaterally to look for asymmetries and focal discrepancies. The infant may exhibit a paucity of spontaneous limb movements, and breathing may be paradoxical, with chest lowering and stomach rising as the result of primarily diaphragmatic strength. Severe respiratory compromise along with profound hypotonia may be features of neonatal spinal cord injury as well as congenital myopathies. A loss of pain sensation below the neck, as evidenced by the absence of facial grimace following a painful stimulation, is suggestive of spinal cord injury. Deep tendon reflexes and the presence of clonus should be assessed in all children and the plantar response elicited in the older child. The presence of contractures is common in congenital muscular dystrophy and congenital myotonic dystrophy. Some infants present with multiple joint contractures (ie, congenital multiple arthrogryposis) resulting from intrauterine anterior horn cell damage. The older child may have developed scoliosis from the effects of gravity on a weak spine. Important clues are the absence of deep tendon reflexes in neuropathies and SMA and the presence of percussion myotonia in myotonic dystrophy. Sensory testing is important in the patient with suspected neuropathy, including hereditary motor-sensory and sensory-autonomic neuropathies, radiculopathies, and myelopathies. The responses to be observed are latency, limb movement quality (more than stereotyped triple flexion), facial grimace and cry, and habituation. Muscle pain on palpation is suggestive of immune or

Box 128.3. Maneuvers to Assess Localized Hypotonia

Head Control (Neck Tone)
- Traction maneuver

Trunk
- Horizontal prone suspension

Shoulder Girdle
- Scarf sign
- Axillary suspension

Extremity Tone
- Popliteal angle

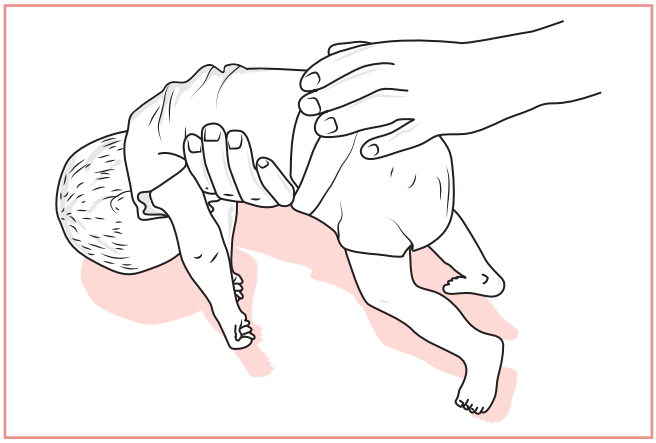

Figure 128.2. Horizontal prone suspension. The head, arms, and legs dangle, and the trunk forms an inverted "U".

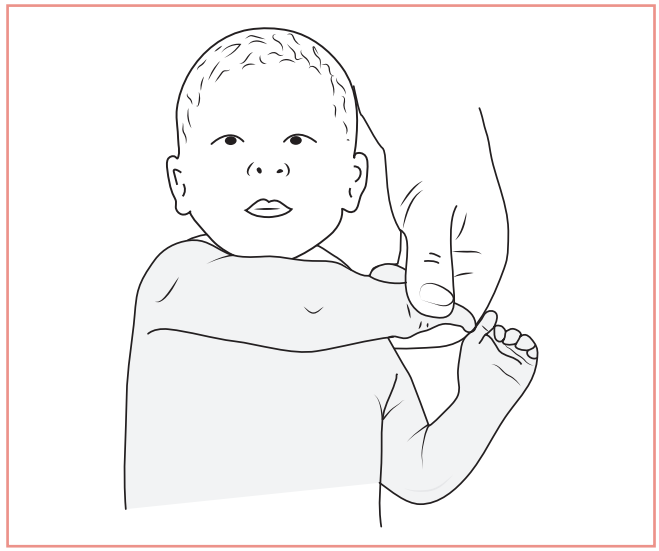

Figure 128.3. Scarf sign. With the wrist pulled gently across the chest, the elbow passes the midline.

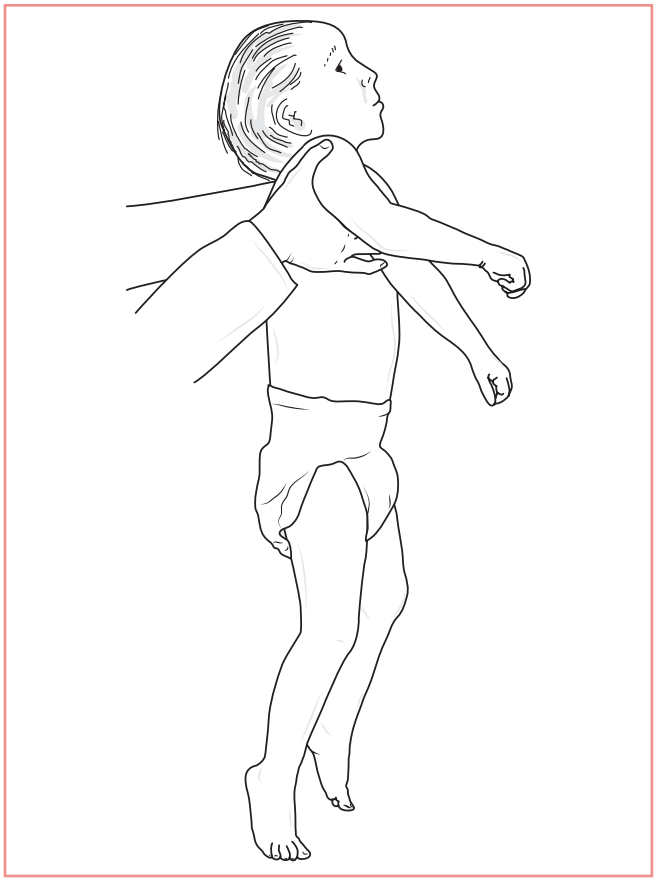

Figure 128.4. Axillary suspension. The infant cannot adduct the shoulders and tends to slide through the examiner's open hands.

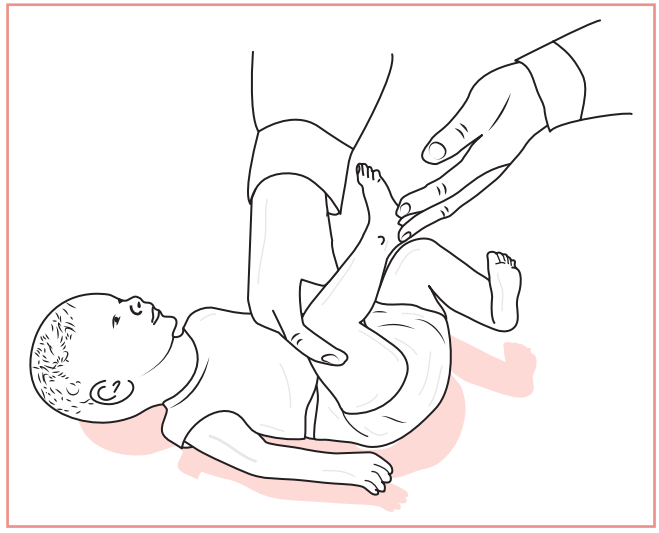

Figure 128.5. Popliteal angle. With the hip maximally flexed, the knee is gently extended maximally while resting on the infant's abdomen. In the infant with hypotonia, the angle of the knee joint is greater than 90° shortly after term birth and greater than 120° at 3 months of age.

infectious, viral, or parasitic myositis. In the neonate with hypotonia, it may also be necessary to examine the mother for the presence of signs of myotonic dystrophy or myasthenia gravis.

Observation rather than formal individual muscle testing is often easier and more revealing, particularly in infants and preschool-age children. Useful activities to observe include walking, running, climbing stairs or stepping onto a stool, lying on the floor and coming to a standing position unassisted, smiling, closing the eyes tightly, and speaking. The ambulatory child may have a waddling gait resulting from hip girdle weakness, genu recurvatum resulting from quadriceps weakness, or talipes planus resulting from foot weakness. Arising from a prone position on the floor, the child may demonstrate the Gowers sign by first getting to the hands and knees, then walking the feet forward to the hands, and finally "walking" the hands up the shins, the thighs, and the trunk to gain an upright position, rather than quickly rising from squatting without using the hands.

Laboratory Tests

Evaluation of the depressed neonate with hypotonia should include an evaluation for infection consisting of complete blood cell count and appropriate cultures as well as an assessment of pH, blood gas,

glucose, electrolytes, liver function tests, ammonia, and amino acids in the blood, and sugars, organic acids, and ketones in the urine. Spinal fluid examination is sometimes helpful in the setting of an increase in white blood cells related to possible infection or inflammation or in the setting of an increased level of protein, as in immune, storage, or necrotizing CNS conditions.

Screening blood or plasma tests can also be important for diagnosis of severe neonatal hypotonia, which can be a result of inborn errors of metabolism (Box 128.4). Serum creatine phosphokinase, a screening test for muscle fiber necrosis, should be requested when the history is suggestive of a degenerative condition or examination is indicative that the cause of hypotonia is in the neuromuscular unit. Creatine phosphokinase is 10 to 100 times higher than normal in children with muscular dystrophy, and it may also be mildly elevated in female carriers of the mutant dystrophin gene in their first 3 decades. The serum creatine phosphokinase level may be less markedly elevated in the child with an inflammatory myopathy, such as dermatomyositis and polymyositis, and to some extent after muscle trauma, unless there is rhabdomyolysis where serum creatinine phosphokinase levels are uniformly elevated.

One purpose of laboratory tests in the child with a neuromuscular condition is to confirm which nervous system level is involved (Table 128.3). Useful information about the presence of neuropathic, myopathic, and neuromuscular junction disorders can be obtained from the nerve conduction velocity and EMG. Demyelinating neuropathies slow nerve conduction or produce signs of a segmental conduction block. If the problem is a motor neuropathy, an axonal neuropathy may have depressed amplitude of the nerve action potential or fibrillation potentials on EMG. In some myopathies, small amplitude potentials and myotonia may be seen on EMG. Decremental response to stimulation and other abnormalities are evident with myasthenia gravis and neuromuscular junction blockade caused by the botulinum toxin. Serology and EMG tests can confirm diagnosis of myasthenia gravis in the child with variable weakness and easy fatigability by history and particularly eyelid or extraocular muscle fatigability on examination. Some neuromuscular conditions are associated with cardiomyopathies and, therefore, electrocardiography and echocardiography can help in diagnosis and identification of potentially critical problems that necessitate acute intervention, such as heart conduction block. Pulmonary function tests may be necessary in the setting of acute acquired myopathies and some severe congenital myopathies. Sleep studies are often helpful in the setting of chronic conditions, particularly myotonic dystrophy.

When done properly, muscle biopsy provides useful diagnostic information about neuromuscular disorders that may cause hypotonia. A large portion of the tissue should be frozen for histochemical studies. With histochemistry, neuropathic changes can be differentiated from myopathic changes related to fiber-type specificities and structural abnormalities that are indicative of dystrophy, glycogen storage disease, or congenital myopathy (eg, nemaline bodies, central cores, central nuclei) can be identified. Histochemical stains can also be informative about metabolic myopathic disorders, and immunohistochemical stains can be used to establish marker evidence for specific diagnoses. Another portion of the muscle should be fixed in glutaraldehyde for evaluation on electron microscopy to determine if ultrastructural abnormalities, such as those that occur in mitochondrial myopathies, are present. Tissue can be subjected to other specific expression analyses, such as dystrophin protein levels, glycolytic enzyme activity, cytochrome-*c* oxidase and other respiratory chain enzyme complex assays, free carnitine and acylcarnitine levels, or fatty acid transport and beta oxidation assays to confirm a diagnosis.

Metabolic and molecular genetic studies can sometimes be done on blood or urine samples, such as thyroid functions if clinical suspicion of hypothyroidism persists; white blood cell enzymatic assays; very long-chain fatty acid profiles for peroxisomal disorders, including neonatal adrenoleukodystrophy; lysosomal enzyme screening tests, such as acid maltase for glycogen storage disease type 2; plasma amino acid levels; and urine organic acid levels. Cytogenetic analysis may be useful when Down syndrome or other chromosomal aberrations are suspected, and DNA methylation analysis is done when Prader-Willi syndrome is suspected as a cause of nonparalytic

Table 128.3. Laboratory Tests Useful Early in the Diagnosis of Hypotonia Caused by Neuromuscular Lesions[a]

	Anatomic Site		
Test	*Anterior Horn Cell*	*Neuromuscular Junction*	*Muscle*
Muscle enzymes	Normal	Normal	Normal/ increased
Electromyography	Neuropathic	Decremental/ incremental	Myopathic
Muscle biopsy	Group atrophy	Normal	Myopathic

[a] If muscle enzymes are high in a chronic condition, gene tests (eg, a sequenced panel) may supplant the need for these tests.

Box 128.4. Etiologies for Severe Neonatal Hypotonia

- Peroxisomal disorders
- Glycine encephalopathy
- Pyruvate dehydrogenase deficiency or other congenital lactic acidosis
- Organic acidemias
- Fatty acid oxidation disorders
- Primary carnitine deficiency
- Maple syrup urine disease
- Molybdenum cofactor deficiency
- Vitamin D-dependent rickets type I
- Magnesium toxicity
- Creatine metabolism disorders
- Hyperammonemic encephalopathies

hypotonia. When examination and screening laboratory tests have narrowed the diagnostic possibilities to a level of the nervous system, molecular techniques, including use of specific nucleic acid probes, comparative genomic hybridization, copy number variance, gene panels, and exon sequencing screening tests, can sometimes be used to help make specific diagnoses for genetic disorders (eg, Duchenne or other X-linked muscular dystrophies, myotonic dystrophies, mitochondrial cytopathies, SMA). Increasingly, use of these blood tests has eliminated the need for painful EMG or muscle biopsy.

Imaging Studies

Brain magnetic resonance (MR) imaging is diagnostically helpful in at least 4 situations: when deficits in mental status, cognitive function, or attention are apparent in the child with hypotonia; when neurologic examination suggests an upper motor neuron component to the weakness or hypotonia, such as active deep tendon reflexes, persistent ankle clonus, or asymmetries in any sign that may be suggestive of a stroke or a space-occupying lesion; when a progressive congenital muscular dystrophy or a mitochondrial cytopathy, such as Leigh disease, is suggested based on myopathic and CNS signs; and when a child exhibits hypotonia as part of a multiorgan dysgenesis, such as with a chromosomal aberration, because of the high likelihood of a brain component to the dysgenesis. Brain computed tomography is rarely helpful except acutely in the setting of trauma or suspected trauma. Muscle MR imaging can be useful in selecting a muscle for biopsy in cases of suspected inflammatory myopathy. Spinal MR imaging may be necessary in the setting of focal weakness, sensory level, and back pain.

Management

Specific management is dependent on the diagnosis but ranges from supportive respiratory measures and anti-inflammatory therapies to physical and orthopedic therapy to improve function. Sometimes the potential for partial or full recovery is an important factor in determining the goals of clinical management and therapy for the child with a neuromuscular condition. An infant with a congenital myopathy may gradually increase in strength and should, therefore, receive intensive supportive care, including long-term ventilatory support and gastrostomy feeding. However, the family of an infant with a rapidly degenerative terminal condition with CNS damage, such as Walker-Warburg syndrome, the severe infantile type of pyruvate dehydrogenase deficiency, or Tay-Sachs disease, may elect not to undertake respiratory support after they understand the course of the disease and lack of curative therapy. Such families usually continue to benefit from the ongoing information provided by the physician and support of paramedical personnel and lay groups, and the affected child can benefit from palliative therapies and hospice care.

Spinal muscular atrophy is caused by mutations in the *SMN1* gene, which codes for the survival motor neuron protein. Nusinersen is an antisense oligonucleotide that modulates mRNA splicing of a closely related gene, *SMN2*, and converts it to a form that produces functional survival motor neuron protein. Another promising agent for treating spinal muscular atrophy uses an adeno-associated virus 9 viral capsid shell engineered to deliver an intracellularly functional survival motor neuron gene. This agent crosses the blood-brain barrier, so it can be administered intravenously.

Adjunctive corticosteroid therapy is useful in the child with Duchenne muscular dystrophy; however, the temporary beneficial effects must be weighed against steroid toxicity. New therapies for providing dystrophin expression are under active investigation, including "exon skipping" promoting drugs and dystrophin gene fragment-carrying viral vectors. Eteplirsen is an exon-skipping drug recently marketed for boys with a mutation in 1 of the most commonly mutated exons producing a stop codon. This drug allows production of sufficient dystrophin to arrest disease progression.

Suspected metabolic disorders can be managed with focused metabolic therapy, such as eliminating a toxic nutrient from feeding; using a high-energy alternative nutrient (ie, glucose or fatty acids); using the ketogenic diet for hypoglycemic or glucose transporter defects; frequent feedings and overnight continuous gastric formula infusions for fatty acid metabolism defects; managing hyperammonemia with benzoate, sodium phenylbutyrate, or arginine or using dialysis when the ammonia level becomes dangerously high; administering insulin to control hyperglycemia; reducing periods of catabolism during an infection; and supplementing vitamin cofactors and carnitine. Enzyme replacement therapy is available for a growing number of storage disorders. Metabolic myopathies are sometimes empirically managed with thiamine, riboflavin, nicotinamide, coenzyme Q10, biotin, L-carnitine, succinate, vitamin C or K, and medium-chain triglyceride oil. In some cases, use of these therapies may be based on tissue analysis.

The child with acquired acute hypotonic weakness may require therapy directed more at the underlying pathophysiologic process than at the weakness (Box 128.5). Acute postinfectious polyneuritis and variants necessitate careful, frequent monitoring of respiratory status and artificial ventilation when significant loss of vital capacity has occurred. Additionally, plasmapheresis or intravenous immunoglobulin should be considered, particularly for the small child whose condition rapidly worsens early in the course of the disorder. Specific antisera are used for botulinum intoxication. In the child with tick paralysis, removal of the tick from the skin results

Box 128.5. Common Neuromuscular Etiologies of Hypotonia Caused by Acute Generalized Weakness

- Acute postinfectious polyradiculoneuritis (ie, Guillain-Barré syndrome)
- Postinfectious myositis, with or without rhabdomyolysis
- Enteroviral poliomyelitis
- Acute myasthenia gravis
- Infantile botulism
- Tick paralysis
- Periodic paralysis (hyperkalemic, hypokalemic, and normokalemic)
- Metabolic myopathy

in recovery in 1 to 2 days. Dysimmune myasthenia resistant to immunosuppressive medication can be managed with anticholinesterase medication, intravenous immunoglobulin, or thymectomy. In addition to more acute disorders, chronic relapsing polyneuritis and myositis can be managed effectively with various anti-inflammatory agents, including prednisone and immunoglobulin, during periods of exacerbation.

The child with profound weakness easily succumbs to respiratory infections and has difficulty recovering from anesthesia; thus, vigilance on the part of the parent or caregiver as well as early intervention are required because the child may need intense respiratory support. Nutritional and gastrointestinal support may be necessary in the setting of a chronic condition. In some instances, the child with long-term neuromuscular weakness may benefit from orthopedic procedures for scoliosis stabilization to prevent respiratory compromise. Many conditions are genetically complex, and families benefit from genetic counseling and consultation.

Currently, treatment and care of the child with muscular dystrophy or another neuromuscular condition is focused individually on maintaining mobility and preventing contractures through physical therapy, bivalve casting, bracing, and surgical repair to improve limb function by joint stabilization or equalizing of muscle strengths across joints. Physical and occupational therapy can accelerate recovery after procedures and maximize function. Inactivity generally increases disability. Many new hardware technologies (eg, long leg brace, electric wheelchair, battery-operated ventilator, noninvasive positive-pressure ventilation for some cases of respiratory insufficiency) have allowed affected children to overcome previously insurmountable disabilities.

Prognosis

Forms of muscular dystrophy without available treatments progress over a variable number of years. Duchenne muscular dystrophy generally progresses to full-time artificial ventilation over the course of 15 to 20 years, but new gene therapies in development may eventually extend the age before full-time artificial ventilation is required. The course of many genetic conditions can be quite variable and related to different alleles at the disease gene locus or different positions of a critical base pair substitution or deletion. For example, SMA and dystrophinopathies involve genes with multiple abnormal modes of expression with widely different prognostic implications for disease course. The disease course of SMA is dependent on the number of copies of the rescue *SMN2* gene present. In DMD, the relentless disease course is produced by a stop codon mutation, whereas in Becker muscular dystrophy a different mutation allows some or partially functional protein to be manufactured. The severity of myotonic dystrophy is dependent on the length of the triple repeat mutation in the gene. Other loci may also have a modifying effect on disease gene expression or the pathophysiology of the disease.

The weakness associated with congenital myopathies, however, usually slowly improves. Acquired toxin and immune-mediated conditions, such as infant botulism and Guillain-Barré syndrome, generally have a good outcome (ie, in up to 85% of patients), although long-term supportive measures may be necessary.

CASE RESOLUTION

The infant was judged to have hypotonia caused by a neuromuscular condition, in part because of her alert appearance and absent deep tendon reflexes. Neuropathic abnormalities on EMG and muscle biopsy were also present. A blood test for the survival motor neuron genes did not detect any normal sequences, confirming the diagnosis of SMA type 1. She had both SMN1 alleles mutated and only 2 copies of the *SMN2* gene. She was begun on an oligonucleotide to support production of sufficient survival motor neuron protein. The family received genetic counseling and became involved in a support group, and the girl made slow motor developmental progress with normal intellectual function. The physician coordinated genetic and neurologic services for the family.

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CHAPTER 129

Headaches

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CASE STUDY

A 12-year-old girl is brought in with a history of headaches. Although she has been sent home from school twice in the past 6 weeks, she has experienced headaches for at least 1 year. The last episode, 1 week prior to this office visit, was typical. The headache began as a dull feeling over both eyes, radiated up to the top of her head, and eventually became pounding. She had no preliminary visual symptoms or other warning signs prior to the head pain. The episode began during an afternoon class after she had been outside on a hot, sunny day for physical education. The headache worsened after she walked home from school. After she got home, she went to her room, drew the curtains, and lay down on her bed. She experienced some nausea and loss of appetite but no vomiting. She did not get up for dinner. She denied experiencing diplopia, vertigo, ataxia, and limb weakness, and her speech was observed to be articulate and coherent. She took 2 80-mg children's acetaminophen tablets without significant relief but eventually fell asleep. The following morning, she felt fine.

Between headaches, her behavior has not changed, and she has continued to make above-average grades. She has not experienced any major changes in her home environment. When initially questioned, her mother denied having migraines but did admit to needing to lie down because of headaches approximately once a month. A detailed neurologic examination of the girl is completely normal.

Questions

1. How do the symptoms and neurologic examination help differentiate headaches caused by an intracranial space-occupying lesion from headaches caused by a chronic migrainous condition?
2. How do the symptoms and neurologic examination help identify the etiology of the headache?
3. What are the characteristics of headaches caused by intracranial tumors and migraines?
4. How do lifestyle and environmental history help identify headache triggers and help in management of the headache?
5. What is the appropriate treatment plan for patients such as the one discussed in the case study?

Headaches, which are quite common in adolescents and older children particularly, frequently prompt parents or caregivers to have their child evaluated by a physician. The physician must differentiate headaches that are symptomatic of a progressive intracranial process from those that may possibly be intermittently disabling but do not necessitate surgery. The cornerstone of this determination is obtaining key historical information and determining whether abnormalities exist on examination of the nervous system. Decisions about management strategies are influenced mostly by etiology and the effect of the headaches on the child's life.

Epidemiology

The contribution of secondary headaches (ie, those related to tumors, vascular abnormalities, or meningitis) to the overall prevalence of headache is relatively small. Chronic nonprogressive headaches in children that are not related to a self-limited condition are frequently lumped together as "migraine," which includes migraine with and without aura. The prevalence of migraine that comes to the attention of a physician is approximately 3% to 10% for all children, although as many as 75% of all children and 85% of adolescents admit to having experienced a headache in the prior year. Although initial headache symptoms begin most often between ages 6 and 12 years, many patients come to medical attention initially during adolescence, especially girls, whose headache prevalence at that age is double that of boys. In adolescents, the prevalence of chronic migraine is 0.8% to 1.8%. Headaches are also commonly associated with trauma, including concussion, acute intercurrent infection, and other systemic illness.

Clinical Presentation

Parents and caregivers must interpret the nature and severity of their child's experience and symptoms, which may be difficult, especially in younger children. Younger children more rarely complain of head pain but more commonly complain of stomachache or present with nausea or vomiting. Later, as the child ages, the same episodic setting and behavior are associated with a headache complaint. The episodic syndromes of cyclic vomiting, benign paroxysmal vertigo, benign paroxysmal torticollis, and abdominal migraine are related presentations of childhood migraine. Adolescents, however, may report persistent, dull, aching, or pounding head pain, which can recur daily. As opposed to headaches that increase in intensity or frequency and are associated with neurologic signs, which may be suggestive

of an intracranial mass lesion, migraine episodes may be relatively stable in frequency over many weeks or months, accompanied by a normal neurologic and ophthalmologic examination, and similar to that experienced by other family members (Box 129.1). A multigenerational family history of "sick headaches" is a frequent finding in the child with migraine. This history must be specifically elicited by the physician, however, because its significance is often discounted by parents. Migraine with aura, which is relatively unusual in children, is distinguished by the presence of reversible specific sensory symptoms (usually visual) that precede the headache. The headaches may be associated with a prodrome of lethargy, irritability, slowness of movement and response, concentration problems, intolerance of intense sound or light, loss of appetite, and typically at least 1 facial autonomic manifestation (eg, conjunctival injection, sweating, periorbital swelling, ptosis, miosis). Migraine has a tremendous capacity to negatively affect a child's schooling, both in attendance and performance while present.

Pathophysiology

Pain fibers are carried in the trigeminal nerves from the scalp, skull, meninges, and vessel walls within the brain. These fibers experience traction or inflammation at their endings, thereby producing the pain that is associated with mass lesions or meningeal inflammation as well as mediating the pain from an internal (brain) pain generator or perhaps an external painfully tense scalp muscle (through a more circuitous route). The "migraine generator" likely resides in the brain stem and has input to the trigeminal nucleus, which both innervates intracranial blood vessels and receives nerve signals from them. "Cortical spreading depression of Leão," the neuronal and glial depolarization wave that may be the electrophysiologic correlate of the migraine aura, also activates trigeminal afferents. One likely pathogenically deficient neurotransmitter at the vascular nerve endings, serotonin, allows a cascade of release of local cytokines, substance P, calcitonin gene-related peptide, and histamine in and around the vessel walls. These substances in turn cause changes in vascular permeability, local extravascular space swelling, and painful inflammation.

The usual distinction between migraine and tension headache pathophysiology is more difficult to make in the child than the adult (and perhaps is less important from a management perspective) and may involve the types of factors that trigger headaches at different ages (Box 129.2). Several different mechanisms result in the triggering of pain nerves involving environmental or internal factors in genetically predisposed individuals. For example, bright sunlight, environmental stress, or a drop in menstrual hormones likely trigger migraines by different mechanisms within the brain. The rare condition of familial hemiplegic migraine has been related to mutations in 3 different genes thus far, illustrating a quite specific predisposition. Most pediatric patients have in their pedigree other individuals who have experienced migraine at some point in their life; however, the relative roles of genetic susceptibility and environmental trigger agents are subjects of much ongoing investigation.

Differential Diagnosis

Acute Headaches

Emergent causes should be considered if headaches have an abrupt onset, rapidly worsen, or are especially severe or if the child describes the headache as a "thunderclap" or "the worst of my life." Intracranial hemorrhage from a ruptured aneurysm or an arteriovenous malformation or, rarely, as a secondary effect of extreme hypertension, is foremost on the list of such causes. If a child has a condition that may potentially result in stroke, such as coagulopathy, hemoglobinopathy, or heart disease, the stroke may become hemorrhagic and produce such an acute, severe headache resulting from sudden traction of pain fibers from space-occupying extravascular blood.

Nonhemorrhagic meningeal irritation, such as the inflammation produced by bacterial or viral meningitis, may also cause acute headache. These conditions may render the patient confused and lethargic while still conscious and often are associated with fever. Both types of meningeal irritation produce nuchal rigidity and Kernig and Brudzinski signs. Less serious viral illnesses outside the nervous system also can produce headache acutely but show other reassuring signs, such as rhinitis, and lack meningeal signs or altered mental status.

Chronic Progressive Headaches

The child with brain tumor or brain abscess or with a gradual block in cerebrospinal fluid (CSF) flow producing hydrocephalus

Box 129.1. Diagnosis of Headaches (Migraine) in the Pediatric Patient

- Head pain of ≥2 hours' duration, often pounding in character, mostly bilateral, over the eyes, at the vertex, or in the temporal region
- Pain frequently accompanied by nausea, anorexia, photophobia, or phonophobia, and aversion to movement
- Pain sometimes preceded or accompanied by visual symptoms, such as scotomas or other sensory or dysphasic auras that fully reverse
- Frequent presence of trigger factors
- Positive family history of headaches

Box 129.2. Triggers of Migraine

- Glare, dazzle, bright sunlight, or fluorescent lighting
- Physical exertion, fatigue, lack of exercise, lack of adequate sleep, hunger or skipping meals
- Change in ambient temperature or humidity
- Allergic reactions involving sinuses, pungent odors
- Certain foods, alcoholic beverages, and cold foods or beverages
- Anxiety, stress, and worry
- Head trauma
- Menstruation and oral contraceptives
- Refractive errors if they produce squinting (unusual)

frequently has a "crescendo" history, usually of less than 6 months' duration, of increasing severity or frequency of headaches. The headache pain may be consistently localized, or it may awaken the patient from sleep, presumably related to relative shift in intracranial traction forces resulting from gravity and the horizontal position. Of note, many children with brain tumors do not complain of a localized headache and may present with persistent vomiting without headache as a prominent symptom. Between headaches children often experience new coordination problems, lethargy, loss of attained skills, personality change, or deterioration of schoolwork. Idiopathic intracranial hypertension (IIH), like intracranial venous sinus obstruction, presents with headaches of recent onset and associated papilledema. Hypervitaminosis A, steroid withdrawal, tetracycline treatment, and obesity have all been related etiologically to IIH, which most commonly occurs in adolescent females.

Chronic Recurrent Headaches

The pain of migraine headaches, the most common chronic headache type, is throbbing in character, and if headaches are severe, patients avoid intense sensory stimuli or even routine physical activity. Episodes may last 2 hours to 3 days but often resolve with sleep. Nausea or dizziness, anorexia, and visual blurring are often associated with migraine headache. The pain may be severe enough to curtail activities, or the child may participate under duress, particularly at school. Migraine with aura is preceded by 10 to 20 minutes of a sensory phenomenon, usually dark spots or visual patterns. The aura may be confused with a transient ischemic attack; however, aura proceeds more slowly and may exhibit positive sensations, such as scintillations or paresthesias.

Sinus infection may be confused with chronically recurring or acute headaches, especially if the pain is facial as well as cranial. Symptoms of chronic nasal congestion may be present with migraine, but allergies and postnasal drip may be associated with sinus headaches. In many cases the infection is a trigger for a migraine headache and the patient has primary migraine, not pain originating from the sinusitis as may have been previously assumed. Children with asthma also have recurring headaches that possibly are triggered by sinus involvement, generalized cytokine release, or other aspects of asthmatic pathophysiology, such as smooth muscle reactivity and susceptibility to medication side effects.

Other types of headache may recur without progression. In some cases, *chronic daily headaches* (ie, >15 headache days per month) may be "transformed migraine" or "rebound headache" resulting from abortive medication overuse. Adolescents may have frequently recurring headaches triggered by irregular lifestyles, such as not exercising enough, eating regularly, or getting adequate sleep, if they are susceptible individuals. In many individuals, symptomatology is more consistent with *tension-type headaches*, which are characterized by a feeling of a tightening band around the head rather than a throbbing pain, an occurrence late in the day, and an association with anxiety, depression, or a stressful environment. These "featureless" headaches are not worsened by routine physical activity or accompanied by nausea, vomiting, photophobia, or phonophobia. Overlap exists in this group with migraine headache symptoms and response to therapy. Posttraumatic headaches may be a significant problem as part of a concussion but should recur with gradually decreasing severity over several days to months.

Cluster headaches are quite different from the other types discussed. They are shorter (ie, ½–3 hours' duration); are associated with unilateral lancinating pain, tearing, nasal stuffiness, Horner syndrome, and nighttime pacing; and are unusual in children, almost never occurring in persons younger than 10 years.

Evaluation

History

Information should be obtained from patients, parents or guardians, and other caregivers concerning when headaches first began; the quality, intensity, and location of headaches; and other associated symptoms before and during headaches (Box 129.3). Duration, clinical course, and conditions that evoke, intensify, or alleviate the pain are also important. It is useful to have the child describe a typical episode—perhaps the most recent—including the circumstances

Box 129.3. What to Ask

Headaches

- Where is the child, what time of day is it, and what is the child doing when a typical headache begins or the last recalled headache began?
- Where is the pain located? How severe is the pain? How long does the pain last?
- Is nausea, vomiting, phonophobia, or photophobia associated with the headache?
- What does the child do after getting the headache? Does the episode require cessation of activities?
- Does the child take any medication for the pain? If so, was it successful? What else, if anything, allows the child to feel better?
- How long ago did the first headache occur? Are headaches becoming more frequent or severe?
- Does the child experience motion sickness?
- Have headaches ever awakened the child at night?
- Does the child have other chronic conditions? Does the child take medications or vitamins?
- Have there been any changes in weight, speech, vision, gait, school performance, or personality or any loss of skills or abilities between headaches? Do all the accompanying symptoms of the headache resolve after each headache episode?
- Does the child have any warning symptoms before the pain? Does unilateral visual loss, weakness or numbness, diplopia, confusion, or loss of consciousness occur with the headache?
- How often does the child miss school because of a headache?
- Are there stressful circumstances or major life changes? Has there been depression or anxiety?
- Do other members of the family have headaches? Do they ever need to lie down or take medicine for these headaches?

of when and where the headache began and how it affected activities at the time. The circumstances of the headache can help determine individual triggers, and the degree to which the headache problem affects the child's lifestyle strongly influences the management plan for chronic recurrent headaches.

Physical Examination

Blood pressure should be noted, even though primary hypertension is an unusual cause of headaches in children. Growth abnormalities and neurocutaneous findings or signs of trauma may be relevant. A thorough neurologic examination is needed to determine if findings suggest an emergent problem, such as meningitis, or a potential neurosurgical condition, such as intracranial hemorrhage or brain tumor. Examination should assess for the presence of sinus, teeth, or temporomandibular joint tenderness; nuchal rigidity; funduscopic abnormalities (eg, papilledema, hemorrhage); signs of trauma; and any focal neurologic signs. Ataxia and cranial nerve signs for a posterior fossa lesion may be indicative of a brain tumor or other space-occupying lesion; loss of visual fields or hypothalamic dysfunction (ie, endocrine abnormalities) may be indicative of a suprasellar or third ventricular region lesion; and hemiparesis, hemisensory deficit, or language dysfunction may be indicative of a cerebral hemispheric lesion. The physician should pay particular attention to personality changes or developmental regression. Increased intracranial pressure (ICP) may lead to papilledema, loss of upward gaze, general hypertonicity, leg weakness, positive Babinski sign, spastic gait, loss of continence, or confusion or stupor resulting from either blockage of CSF by the tumor or by blocking of blood drainage from intracranial sinus occlusion or by IIH. Because the presence of papilledema is so informative, all children with headaches should undergo a fundus examination.

Rarely, during a migraine headache a child may exhibit confusion, aphasia, unilateral numbness, or, less commonly, weakness, hemianopsia, or perceptual distortion (ie, "Alice in Wonderland" syndrome). In these circumstances, diagnosis of complications of a migraine or a migraine syndrome is reached only after diagnostic tests have eliminated other acute encephalopathies.

Laboratory Tests

If stiff neck and fever are present and focal or lateralized neurologic signs are absent, an immediate CSF examination is indicated to diagnose the cause of meningeal inflammation, particularly in the child with immunodeficiency. When hemorrhagic fluid is encountered, it is often useful to centrifuge a specimen to check for xanthochromia and to count cells in a subsequent sample to differentiate a traumatic spinal tap from subarachnoid hemorrhage. If papilledema is present and imaging studies are normal, a lumbar puncture should be done to measure CSF pressure.

A sleep study may be indicated if the child has a history of obstructive snoring or recurrent sleep disruption.

Imaging Studies

Recent trauma; persistent vomiting; depressed alertness; crescendo or change in pattern; or chronic conditions, such as sickle cell disease, coagulopathies, neoplasms, neurocutaneous syndromes, cyanotic heart disease; and even recent onset of headaches, all may be indications for an immediate head magnetic resonance (MR) imaging (preferable) or computed tomography (CT). The risk of missing an anatomic diagnosis should be weighed against the risk of anesthesia for the study and perhaps false reassurance from an inadequate study. Such decisions are also influenced by the reliability and ease of communication with the child's caregivers. The yield of imaging is low in the absence of neurologic signs. If signs or symptoms of increased ICP are apparent, CT or MR imaging must be obtained to help diagnose the etiology of the headaches. New focal or general neurologic signs or signs of meningeal irritation or encephalitis also indicate the need for CT or MR imaging. Computed tomography angiography or invasive cerebral angiography may be necessary in rare instances to locate a focal source of subarachnoid hemorrhage, and MR venography may help diagnose dural sinus thrombosis. Head imaging studies are also helpful with the diagnosis of chronic or recurrent sinus headaches and Chiari type 1 malformation.

Management

The presence of progressive symptoms, abnormal neurologic signs, or a hemorrhage or space-occupying lesion on an imaging study usually necessitates a neurologic or neurosurgical consultation. It may be necessary to urgently initiate measures for managing increased ICP. In the absence of a mass, increased ICP related to IIH also requires treatment. A serious sequela of IIH is eventual loss of vision if pressure is not relieved. This complication can be monitored with visual field testing and optical coherence tomography. Therapies include CSF withdrawal as a temporizing measure, diuretics (eg, acetazolamide), a weight loss program if obesity is present, and potentially surgical CSF diversion.

If a careful assessment has revealed no acute or progressive conditions, pain is not severe, frequency is low, duration is short, and effect on lifestyle or daily activities is minimal, reassurance is often the appropriate management. Frequently, parental or caregiver anxiety about a potential mass or hemorrhage far outweighs the morbidity produced by the headache symptom itself. Sometimes placing the child's headache problem in context with the parent's/guardian's or other family member's headaches will help with reassurance, and sometimes in milder cases, nonpharmacologic or nonprescription medication strategies can be agreed on as a management plan. Education and sometimes a headache diary or log helps patients and their families take control and own their own problem (ie, discern triggers and track intervention efficacy), particularly when they can correlate headaches with inadequate exercise, skipping meals, inadequate hydration, and inadequate sleep.

It may be apparent, however, that the headaches have produced significant discomfort or disruption of activities or lifestyle for the child and that more than reassurance is needed (Table 129.1). Nevertheless, with any intervention the physician always should weigh side effects against effectiveness of treatment and the possibility of medication overuse headache if the abortive treatment is taken more frequently than twice per week. A goal is a reduction in

Table 129.1. Drugs Useful in Managing Childhood Headaches

Drug Type	*Drug*	*Dosing*
Abortive (symptomatic)	Acetaminophen, PO	325–650 mg every 4 hours (15 mg/kg/dose); alternatively, if ≥12 years, 1,000 mg of long-acting every 6 hours Maximum: 5 doses regular/24 hours or 3,000 mg long-acting/24 hours
	Acetaminophen + acetylsalicylic acid + caffeine	1 dose every 4 hours if ≥12 years of age
	Ibuprofen, PO	200–800 mg every 6 hours (10 mg/kg/dose) Maximum: 40 mg/kg/24 hours
	Naproxen, PO	5–7 mg/kg/dose every 8–12 hours Maximum: 15 mg/kg/24 hours
	Sumatriptan succinate[a] PO, IN, or SC	25–100 mg PO[b] (25 mg PO for children age 6–10 years; may repeat after 2 hours); or 5–20 mg IN (may repeat after 2 hours); or 6 mg SC (may repeat after 1 hour) Maximum: 2 doses/24 hours
	Rizatriptan benzoate, PO	5–10 mg orally disintegrating or regular tablets; may repeat after 2 hours Maximum: 3 doses/24 hours
	Isometheptene mucate with dichloralphenazone and acetaminophen, PO	1–2 capsules at onset; may repeat every 1 hour up to a maximum of 3–5 capsules/day
Status migrainous	Prochlorperazine, IV	5–10 mg single dose (for children age 12 and older) 0.1–0.15 mg/kg/dose (for children less than 12 years)
	Dihydroergotamine mesylate, IV	Age 8 years or younger or weight <25 kg (<55 lb): Test dose of 0.25 mg. After waiting 30 minutes, administer 0.5 mg. Every 8 hours after that, infuse 0.5 mg over 3 minutes. Age 9 years or older or weight ≥25 kg (≥55 lb): Test dose of 0.5 mg. After waiting 30 minutes, administer 1.0 mg. Every 8 hours after that, infuse 1.0 mg over 3 minutes. (Give metoclopramide hydrochloride with initial dose.)
	Dexamethasone, IV	4–16 mg single dose (0.25 mg/kg) or rapidly tapering every 6 hours
Prophylactic	Propranolol	Weight ≤35 kg (≤77 lb): 10–40 mg 2–4 times/day Maximum: 40–80 mg/24 hours
		Weight >35 kg (>77 lb): 120–160 mg/24 hours Maximum: 320 mg/24 hours
	Cyproheptadine hydrochloride	1–4 mg 2–4 times/day (0.25–0.5 mg/kg/24 hours) Maximum: 16 mg/24 hours
	Amitriptyline hydrochloride	5 mg at bedtime for children age 6–12 years; 10 mg at bedtime for children older than 12 years. The dose may be increased by 5–10 mg every 2–3 weeks up to a maximum of 75 mg at bedtime until headaches improve or the child experiences persistent daytime sleepiness.
	Verapamil hydrochloride	Age 1–5 years: 40 mg every 8 hours Age ≥6 years: 40–80 mg every 8 hours
	Divalproex sodium (ie, valproic acid)	10–15 mg/kg/day initial dose, followed by 20–30 mg/kg/day maintenance dose, divided twice/day or administered once every day if extended release Maximum: 60 mg/kg/day (follow clinical signs of toxicity and serum level) Avoid use if pregnancy may occur
	Topiramate	50–200 mg/day divided twice/day after increasing from 25 mg once/day every 2 weeks
	Levetiracetam	20 mg/kg divided 2 times/day; may increase to 60 mg/kg/day
	Gabapentin	4 mg/kg/day divided twice/day, increasing to 8 mg/kg/day after 1 week Maximum: 20 mg/kg/day
	Vitamin B_2 (ie, riboflavin)	25–400 mg/day
	Melatonin	3 mg at bedtime

Abbreviations: IN, intranasally; IV, intravenously; PO, orally; SC, subcutaneously.

[a] Not approved for children less than 6 years.

[b] Only approved route in children 6-10 years.

headache frequency, severity, duration, or disability with improved quality of life. Typically, the initial trial should consist of acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), unless prior use of these medications has been unsuccessful. Abortive treatment should be initiated as soon as possible after the onset of prodromal or headache symptoms. Many children who are allowed medication at school and may lie down for 30 minutes can finish the school day. Naproxen is beneficial, particularly in the child with head or neck muscle or scalp tenderness. Naproxen can be used prophylactically for premenstrual migraine, and indomethacin may be used in the management of unilateral continuous pain with autonomic symptoms (ie, hemicrania continua). Headache in adolescents is sometimes helped by isometheptene mucate. For severe, recurrent headaches, 5-hydroxytryptamine, serotonin$_{1B/1D}$ receptor agonists (ie, triptans) are useful. Sumatriptan succinate and other triptans, which decrease calcitonin gene-related peptide levels, sometimes have relatively tolerable but occasionally anxiety-provoking immediate side effects, including tingling and chest pressure, and patients must be informed of these side effects. The combination of acetaminophen, acetylsalicylic acid, and caffeine compared favorably with sumatriptan succinate in a clinical trial of adolescents. Sumatriptan succinate in combination with naproxen may have increased efficacy compared with either sumatriptan succinate or naproxen alone. Dihydroergotamine mesylate, zolmitriptan, or sumatriptan succinate given intranasally along with promethazine hydrochloride given rectally are also effective abortive treatments in vomiting patients and work faster than tablets; however, the nasal drugs may have a disagreeable taste should they enter the posterior oropharynx. Particularly severe refractory headaches may respond to intravenous (IV) diphenhydramine, ketorolac tromethamine, or prochlorperazine or IV dihydroergotamine mesylate (given after a test dose for hypersensitivity and with an antiemetic) or dexamethasone if IV prochlorperazine is unsuccessful.

The decision to begin a prophylactic medication should be based on the frequency and severity (eg, missing school time) of headaches and failure of abortive medications. Anticonvulsant agents, such as valproic acid, topiramate, levetiracetam, and gabapentin, have been found to be successful antimigraine agents. Valproate sodium has appetite-stimulating and teratogenic effects. The beta blockers, including propranolol, have demonstrated efficacy as prophylactic agents but should be avoided in patients with asthma or depression, and the antihistamine cyproheptadine hydrochloride has been used successfully in many younger patients but is also an appetite stimulant. Amitriptyline hydrochloride and nortriptyline hydrochloride are effective preventive treatments in older children and adolescents; initially, a single bedtime dose should be used. Amitriptyline hydrochloride can be combined with propranolol if necessary. Calcium channel blockers, such as verapamil hydrochloride, may also be useful in older children and adolescents. Isolated success has been achieved with riboflavin, magnesium, botulinum toxin injections, and greater occipital nerve block. With any of the prophylactic medications, a 2- to 4-week trial is necessary before concluding that the initial treatment has proved to be ineffective. With most agents, the dose can be slowly increased to efficacy according to patient tolerance. In patients undergoing prophylactic therapy, the medication should be periodically withdrawn to ascertain whether continuation of the therapy is necessary.

For many of the aforementioned agents, weak evidence that is either anecdotal or from small studies supports their use in childhood migraine. As a result, the Childhood and Adolescent Migraine Prevention (CHAMP) trial was begun in 2012. In this randomized double-blind study, children age 8 through 17 years were recruited and assigned to 1 of 3 arms: amitriptyline hydrochloride (goal dose of 1 mg/kg), topiramate (2 mg/kg), and placebo. Children with continuous headache, medication overuse headache, a very high Migraine Disability Assessment score, psychiatric disease, or who were presently taking 1 of several classes of medications were excluded. The trial was stopped prematurely for futility, because neither test agent was superior to placebo in reaching a positive outcome, which for all 3 arms was an approximately 60% rate of having a 50% reduction in headache days. The test agents had a greater rate of adverse events than placebo, so they could be judged inferior. Perhaps a learning point for the quite high placebo effect in this trial is that all participants received monthly lifestyle migraine management advice and optimal acute therapy, including NSAIDs and triptans and frequency guidance, which reduce the risk of progressing from episodic to chronic migraine and may have had a preventive role in this trial. Despite the potential negative conclusion about prophylactic medication from this trial, a utility for prophylactics may still exist in cases in which the acute treatment cannot practically be as optimal as in the trial, the side effect potential is quite low (such as with melatonin, riboflavin, or lower doses of prescription medications [eg, amitriptyline hydrochloride at a 10 mg dose]), or the patient has 1 of the first 3 trial exclusion criteria (ie, continuous headache, medication overuse headache, very high Migraine Disability Assessment score).

Chronic daily headaches may be successfully managed with education, use of prophylactic medication, and avoidance of abortive analgesics in the patient who experiences transformed migraine resulting from rebound effects. In fact, medication overuse headaches often benefit solely from abstinence for 1 to 2 weeks. Some children need assistance returning to a functional daily routine or a program for restoring school attendance. Healthy lifestyle changes and learning how to manage stress by relaxation training have been very beneficial, particularly in adolescents (as seen in the CHAMP trial); however, biofeedback-assisted guided imagery, hypnosis, meditation, and acupuncture have limited availability and high cost. If either severe environmental stressors or psychological trauma serve an ongoing headache trigger, the patient may benefit from psychotherapy.

Prognosis

Many children with headaches have a good prognosis and do not require ongoing intervention after families are reassured of the benign nature of the problem. For other children, appropriately used abortive medications alone are frequently effective. The prognosis

is less positive in children with headaches with psychiatric comorbidity. Pediatric patients, especially boys, frequently experience complete remission of their headaches by adolescence, and, by adulthood, the incidence of headaches has decreased in both sexes. A study of more than 100 children reported that chronic headaches persisted after 8 years in only 12%.

CASE RESOLUTION

The child's symptoms and circumstances of the headache suggest a diagnosis of migraine. No laboratory tests or imaging studies are necessary. The girl is begun on amitriptyline hydrochloride and instructed to keep a calendar of headache occurrences. She has 2 headaches in the first 2 weeks, which are aborted effectively with ibuprofen. She has no further recurrences, and the amitriptyline hydrochloride is withdrawn successfully after 3 months.

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CHAPTER 130

Tics

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CASE STUDY

An 8-year-old boy has unusual recurring behaviors that began 2 to 3 months prior to this office visit. He stretches his neck or raises his eyebrows suddenly several times a day. Sometimes he can suppress these actions. The boy's parents report that in the past 2 years he has displayed several repetitive behaviors, including blinking, grimacing, rubbing his chin on his left shoulder, making a "gulping" sound, and sniffing. Originally, they thought the sniffing was related to hay fever, but the boy has no other allergic symptoms. He does not use profane words. In conversation, he sometimes repeats the last phrase of a sentence that was just uttered by himself or someone else. Additionally, he must touch each light switch in the hallway every time he leaves his room, and he must retie his shoelaces several times until they are exactly the same length. Although his schoolwork has not deteriorated, he has always had trouble completing tasks and finishing homework. His teacher and his best friend have asked about his strange behavior. His mother has a "psychological" problem with her son's gulping sounds (ie, they recur in her own mind), and she recalls that her father had a habit of frequently looking over 1 shoulder for no apparent reason.

Although during examination the boy does not exhibit any unusual behaviors, he raises his eyebrows twice and places his hand over his mouth several times while his parents are interviewed. Except for mild fine motor incoordination, the neurologic examination is normal.

Questions

1. What are the characteristics of tics?
2. What are some of the other challenges that children with Tourette syndrome may face?
3. What are the considerations in the management of tic disorders?
4. What other problems are associated with Tourette syndrome that also warrant intervention?

A *tic* is a brief, abrupt, nonpurposeful movement or utterance. Tics occur in a background of normal activity and are repetitive and involuntary but can be suppressed. Tourette syndrome (TS) is the most common etiology of tics in children. It is defined by multiple types of tic displayed over time, including motor tics and vocal tics. Tourette syndrome most frequently manifests solely as a nondisabling movement disorder but may also be associated with other neurobehavioral problems, which may include attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, mood and rage disorders, anxiety, personality and conduct difficulties, and sleep disorders.

Epidemiology

Tics are relatively common in children but often go unrecognized as a movement disorder. The onset of tics associated with TS is generally between 5 and 12 years of age but can be as late as 21 years of age. The prevalence of tics is 5 times higher in males than females. By various estimates, TS prevalence is between 0.1% and 3%, and many cases of TS are familial, with some features occurring in a parent in up to 25% of cases. Family members may have had such mild symptoms that they never sought medical attention. The risk of TS in a sibling is approximately 8%. Tics are more common in male family members, but other family members may have only non-tic manifestations of the syndrome, such as obsessive-compulsive symptoms, which occur most often in females. Tourette syndrome appears to be less common among sub-Saharan Africans and African-Americans.

Clinical Presentation

Children with tics display sudden repetitive movements of the face, neck, shoulders, or hands in the context of normal behaviors, and normal behaviors are sometimes used to mask the tics. Sometimes tics can be suppressed when they would be embarrassing or during a time of intense physical activity, concentration, or performance, but they also may be worsened by stress or strong emotions. Tics associated with TS vary in their manifestations over periods of weeks to months. Some examples of tics are blinking, eye rolling, grimacing, neck stretching, head turning or shaking, shoulder shrugging, stomach tensing, and wrist flicking. Many affected children describe a brief premonitory sensation, which is an indescribable, uncomfortable feeling that is subsequently relieved by the motor tic. Tics may bizarrely mimic normal, sometimes complex, movements or postures or involve a series of orchestrated simple movements, such as sequential finger flexing, wrist bending, and arm stretching. Tics may include sudden repetitive sounds from the vocal apparatus (Box 130.1), which may be produced by a sudden

Box 130.1. Diagnosis of Tics

- Sudden, brief uncontrolled movements
- Repetitive sounds from the vocal apparatus
- Behaviors occurring in the context of or mimicking normal behaviors but having no purpose

movement of air or saliva within the larynx or pharynx or a clicking of the tongue or teeth. Sounds may include throat clearing, sniffing, grunting, squeaking, sucking, or blowing. Additionally, children with TS may also have socially inappropriate words or gestures or repeat a new word or phrase or a word or phrase they have just said or heard.

Children with TS may have learning problems, including easy distractibility and inability to finish schoolwork. Less frequently, they also have intrusive or repetitive thoughts, unfounded fears, or ritualistic actions that may involve touching, cleanliness or neatness, counting and exactness, symmetry or evenness, or irrational checking. Sleep disturbances are not unusual.

Classifications of tics according to the nature of the action can be helpful in understanding apparently widely different movements as being part of the same disorder because of ultimately shared central nervous system chemistry or circuitry (Box 130.2). Clonic tics are brief, and dystonic tics are more sustained movements. In addition to simple tics, patients may rarely have other unusual behaviors (ie, complex tics) including echopraxia (ie, repetitive gestures), copropraxia (ie, obscene gestures), and coprographia (ie, obscene writing). Unusual speech patterns include irrelevant or nonsense words, palinphrasia (ie, repeating one's own words), echolalia (ie, repeating another's words), and coprolalia (ie, obscene speech). Diagnosis is often delayed because of misunderstandings about the common and uncommon manifestations of TS (Box 130.3).

Box 130.2. Types of Tic in Children With Tourette Syndrome

Simple

- Clonic
- Dystonic

Complex

- Series of different or similar simple tics
- More complicated coordinated movement
- Copropraxia and coprographia

Vocal

- Oropharyngeal, nasopharyngeal, or laryngeal sounds
- Consonants or syllables
- Meaningless or nonsense words or phrases
- Coprolalia
- Palinphrasia and echolalia

Box 130.3. Misconceptions in Diagnosing Tourette Syndrome

- Attributing the unusual tic symptom to attention-getting or emotionally based behavior
- Diagnosing the episodic behavior as a seizure based on inadequate historical information
- Attributing a vocal tic to an upper airway, sinus, or allergic condition
- Attributing an ocular tic to an ophthalmologic problem
- Requiring observation of the tics in the office before making the diagnosis
- Waiting for coprolalia to be present before making the diagnosis
- Assuming severe tics are necessary for the diagnosis, or assuming mild tics are a normal developmental phase

Pathophysiology

Tics are thought to be generated from a functional abnormality of circuitry in deep brain nuclei that might include the striate nuclei, globus pallidus, subthalamic nuclei, and substantia nigra. The prefrontal cortex, thalamus, and limbic systems may also be involved. Tourette syndrome, including the generation of the tic movement disorder, must result from several brain-expressed genes with a developmentally influenced expression interacting in a complex manner with psychosocial and other environmental factors and thus making it a true neuropsychiatric condition.

Dopaminergic disinhibition within the circuitry is likely to be part of the abnormal function because of 1 class of medication (eg, stimulants) worsening the symptoms and another class (eg, dopamine antagonists) effective as a treatment. In patients with TS, the cerebrospinal fluid contains low baseline levels of homovanillic acid, a dopamine metabolite, which could result, as has been hypothesized, from a hypersensitive dopamine receptor. Additionally, amphetamines and methylphenidate hydrochloride increase dopamine release, and in some instances, these agents precipitate tic symptoms. Haloperidol, an effective tic-suppressing medication, blocks dopamine receptors and, therefore, may block a potentially hypersensitive Tourette dopamine receptor. The observation of a good clinical response with relatively low doses of dopamine blockers (eg, haloperidol) and the finding of increased homovanillic acid levels resulting from receptor desensitization long after disappearance of the drug support this hypothesis. The physiology is undoubtedly more complex, because medications involving other transmitters also are effective. Rare genetic causes of TS are mutations in the *SLITRK1* gene, which is involved in dendrite growth, and the gene for histidine decarboxylase, *HDC*. Histamine decarboxylase converts histidine to histamine in histaminergic neurons found in the posterior hypothalamus but connecting widely in basal ganglia and other brain regions. It is unknown how either of these genes causes symptoms, and the genetic basis of TS remains elusive.

An observed association of the sudden onset or exacerbation of obsessive-compulsive or tic symptoms with preceding group A

streptococcal infections of the pharynx has been termed pediatric autoimmune neuropsychiatric disease associated with streptococcus (PANDAS). Although for some time it has been known that a clear relationship exists between the same bacteria and another movement problem, Sydenham chorea, the evidence for causality or any role of the bacteria or of related autoimmunity is conflicting and unconfirmed by large studies involving TS or obsessive-compulsive disorder; therefore, routine screening or prophylaxis has not been recommended when these diagnoses or PANDAS are being considered.

Differential Diagnosis

The duration, frequency, and appearance of the movement, the premonitory sensation, and circumstances of occurrence of tics help distinguish them from several other episodic movement disorders. *Myoclonus* is a lightning-like, nonsuppressible jerk of a small group of muscles, and *chorea* involves nearly constant, small amplitude movements of the fingers, hands, and feet that are often accompanied by grimacing movements of the face. *Tremor* is an oscillatory movement of an extremity or the head. *Hemiballismus* is an uncontrollable episodic throwing movement of an extremity. *Hyperekplexia* is a hyperactive startle response provoked by touch or sudden noise. *Torticollis*, or neck writhing, may be paroxysmal but is generally part of a benign transient disorder or a chronic degenerative disorder, such as familial dystonia. *Paroxysmal kinesigenic choreoathetosis*, an unusual episodic condition precipitated by a sudden movement, is characterized by a twisted trunk and limb posture lasting a few seconds (longer than tics, generally) and not accompanied by loss of consciousness. Hypnagogic jerks and bruxism are persistent normal variant behaviors that occur in sleep.

Other repetitive behaviors are sometimes confused with tics. A *compulsion* is a complex action that is done against an individual's will or better judgment. A *stereotypy* is a persistent repetitive senseless movement. A *perseverative behavior* involves continued activity after the cause of it has ceased. The most common self-injurious behaviors are biting or banging of a body part during periods of agitation. An *addictive behavior* occurs with psychological dependence caused by a reward system. A *habit* is a fixed practice established by repetition. A *mannerism* is a stereotyped movement or habit peculiar to an individual and part of that individual's personality. An *anger outburst* is a sudden emotion-generated behavior occurring with relatively little provocation.

Tic disorders are sometimes divided into 3 groups: *simple transient tics*, which are monomorphic (ie, always the same appearance over a period of months), last less than 12 months, and may be caused by particular environmental situations or psychological states; *chronic tics*, which last longer than 12 months but are of a single type; and the tics of TS (Box 130.4). All 3 types of tic disorders may occur in the same family. Tics can also be seen in association with Huntington disease, neuroacanthocytosis, Sydenham chorea, infectious encephalitis, carbon monoxide poisoning, stroke, schizophrenia, head trauma, static developmental encephalopathies, and drug reactions, particularly stimulants, anticonvulsant agents, and antipsychotic agents.

Box 130.4. Conditions Necessary for Diagnosis of Tourette Syndrome

- Multiple motor and vocal tics variably manifested over time
- Tics present for ≥1 year
- Onset of tics before 21 years of age
- Tics not caused by another known condition or substance

Evaluation

History

A thorough history should be taken when evaluating a child with potential tic disorder. The physician should learn as much as possible about the duration, circumstances of occurrence, and frequency of the movements (Box 130.5). Parents or guardians may imitate the behavior or, if possible, bring in a video recording of the child's behavior. This may give the physician more telling information than verbal descriptions. The physician should suggest an array of tic behaviors, because the parent or guardian may not be aware that these behaviors could be tics.

Physical Examination

Frequently, tics are not seen by the physician when observing the child during the examination because the child is able to suppress them; however, the physician may be able to observe the child unobtrusively while still in the waiting room or during the course of the parent/guardian interview. As part of the examination, screening of cognitive abilities and fine-motor coordination should be included because of the comorbidity of ADHD, learning disabilities, and associated fine motor dysmaturity.

Laboratory Tests

No definitive diagnostic or supportive laboratory tests exist for tics generally or TS specifically. Any child with atypical or ambiguous

Box 130.5. What to Ask

Tics

- For how long and how often has the child been displaying the unusual behaviors?
- In what circumstances do the unusual behaviors occur? For example, do the behaviors occur when the child is eating or sleeping, engrossed in an activity, or excited? Or do they occur when attention is on the child or after a startle or other triggering behavior?
- Can the parents or other caregivers imitate or show a video recording of the child's unusual behavior?
- Can the child suppress the behavior?
- Does the child have an uncomfortable premonitory sensation just before the motor tic that is relieved by the tic?
- Is the child having difficulty at school, whether cognitive or social?

movement disorders should be screened for potential metabolic abnormalities, including routine determinations of calcium, magnesium, glucose, liver function enzymes, and ceruloplasmin levels (for Wilson disease). Thyroid function tests may also be requested in the setting of other signs or symptoms of thyroid dysfunction.

Imaging Studies

Research studies of patients with TS have demonstrated volumetric increases in left frontal grey matter thickness and the anterior parts of the corpus callosum and decreases in the caudate nuclei in magnetic resonance imaging studies, as well as increased premotor and cerebellar and reduced resting basal ganglia and orbitofrontal cortex activity in positron emission tomography studies. These imaging modalities have not yet proven clinically useful in the care of individual patients, however.

Management

Goals of management should include reduction in the frequency of tics, especially during critical circumstances, with a minimum of medication side effects and attention to other coexisting learning or behavioral disabilities. Before physicians prescribe drug treatment, they must consider the severity of the tic disorder; the local pain it might be producing from muscle, tendon, or joint stress—forceful neck tics have been associated with cervical spine, vertebral artery, and myelopathic injuries; and its potential for production of psychosocial disability, including family, peer, and school relationships. Some children do not need medication for the movement disorder, and they and their families can be reassured by an understanding of the problem. Other children may experience bullying, recess altercations, or incorrect teacher judgments. Successfully treated patients may also experience remission of their disorder for weeks or months, during which time it is appropriate to reduce or discontinue their medications. Several classes of drugs are useful in the management of tic disorders. Clonidine is indicated for mild cases because of its fair efficacy, good side-effect profile, and convenience. This α_2-adrenergic agonist is available in tablet form and as a transdermal skin patch. Dosage is titrated by effective tablet strength or size and strength of the patch. Guanfacine hydrochloride, an oral formulation in the same class, is also effective and may be less sedating than clonidine tablets. The most direct therapy for the troublesome tics but one that produces more sedative side effects is the dopamine-depleting tetrabenazine. Dopamine blockers, such as pimozide and fluphenazine, can produce tardive dyskinesia, and electrocardiography is recommended before beginning these medications because they have been associated with long QT syndrome; additionally, concomitant use of inhibitors of CYP3A liver metabolism is not recommended. Atypical antipsychotic agents, particularly risperidone, have also been effective, with reduced sedation and potential for extrapyramidal side effects but with increased propensity to cause weight gain and glucose intolerance. Haloperidol has long been used in divided doses starting as low as 0.5 mg per day up to 2 to 6 mg per day but also carries a small risk for tardive dyskinesia. With any of these medications, the child should begin with a low dose that is titrated up to efficacy or the development of intolerable side effects. Botulinum toxin type A injections may be useful for isolated persistent tics involving muscles that are needle accessible. Habit reversal training or comprehensive behavioral intervention for tics has a growing body of supportive evidence; however, such treatment involves a time commitment of child and parents/guardians, the proximity of a trained professional to teach the technique, and an expense that may not be covered by insurance. Nevertheless, the absence of medication side effects has resulted in growing interest in such treatment.

Treatment of the child with TS should be multimodal and prioritize, address, and monitor all problematic aspects of the syndrome (Box 130.6). Up to 60% of children with TS have learning disabilities, including ADHD, and learning disabilities may be a bigger problem for the child than the tics. An assessment is necessary when school performance is suboptimal. Interventions may include organizational aids, homework time management, reduction in potential environmental distractions, and more individualized instruction. Pharmacologic therapy may include clonidine, a tricyclic antidepressant, atomoxetine hydrochloride, or a stimulant. Long-acting methylphenidate hydrochloride or mixed amphetamine salt preparations are not necessarily contraindicated in children with TS; these drugs do not worsen tics in all patients. Children with TS

Box 130.6. Therapies Useful in Managing Tourette Syndrome

Tics

- Clonidine (tablet or transdermal patch): α_2-adrenergic agonist
- Risperidone (low dose): serotonin dopamine receptor antagonist
- Haloperidol (low dose): dopamine receptor blocker
- Pimozide (Orap): dopamine receptor blocker
- Fluphenazine: dopamine receptor blocker
- Guanfacine hydrochloride (Tenex): α_2-adrenergic agonist
- Habit reversal training

Attention-Deficit/Hyperactivity Disorder and Learning Disability

- Clonidine (tablet or transdermal patch): α_2-adrenergic agonist
- Methylphenidate hydrochloride: if tics are not worsened
- Atomoxetine hydrochloride: norepinephrine transporter inhibitor
- Desipramine hydrochloride: tricyclic antidepressant
- Education interventions: individualized or small-group instruction or "504 plan" of accommodations

Obsessive-Compulsive Disorder

- Fluoxetine hydrochloride (Prozac): serotonin uptake inhibitor (nontricyclic)
- Clomipramine hydrochloride (Anafranil): tricyclic antidepressant

Depression and Adjustment Problems

- Psychotherapy (individual and family)
- Imipramine: tricyclic antidepressant
- Support group

also may exhibit symptoms of obsessive-compulsive disorder, although this finding is much less common than learning disabilities. Fluoxetine hydrochloride, sertraline hydrochloride, and clomipramine hydrochloride are useful in managing this comorbidity.

In its severe form, TS may be socially devastating and provoke secondary frustrations, low self-esteem, depression, and other emotional problems as well as the primary psychobehavioral difficulties that may be part of the syndrome. Children with TS and their families frequently benefit from lay educational materials about TS, support groups composed of other families that have children with the syndrome, and local chapters of the Tourette Association of America (https://tourette.org). Referral for psychological or psychiatric counseling for patients and their families may also be necessary, however.

Prognosis

In most children, the prognosis for waning of the tics by adolescence is good, with 50% of tics disappearing by then. Of children who are symptomatic in grade school, less than 20% continue to exhibit clinically significant tic symptoms in older childhood and adulthood. Some children whose tics are exacerbated by psychosocial stressors, however, may have ongoing problems with school success and developing solid peer relationships. If present, these issues should be addressed early in childhood; as with other neuropsychiatric conditions, educational and social problems may be harder to reverse later in life, and the psychological adjustments become important in the long-term prognosis.

CASE RESOLUTION

The boy is diagnosed as having TS. After a discussion with his family about the syndrome, he is treated with Catapres patches. A questionnaire is sent to his teacher concerning ADHD symptoms at school. At a 6-week follow-up visit, he has fewer tics and is doing better in school, having been placed in a classroom with only 15 other students for most of the day.

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CHAPTER 131

Seizures and Epilepsy

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CASE STUDY

A 6-year-old boy is evaluated for unusual episodic behaviors. The previous week his mother was awakened by the boy's brother and found her son lying in bed unresponsive and drooling, with his head and eyes averted to the right, his right arm slightly raised, and his body stiff. His face was jerking intermittently. When the paramedics arrived, the boy's posturing and movements had stopped. After the event, he could speak but was somewhat incoherent. He was taken to the local emergency department, where his examination and mental status were normal. Screening blood and urine tests were normal, and he was discharged with instructions to see his pediatrician for further recommendations.

His father remembers 2 or 3 other episodes of a somewhat different nature in the past month. These occurred as the boy was being put to bed. They involved some body stiffening and facial grimacing, with the mouth slightly open and the tongue twisted and deviated to one side. The child could not speak but appeared to be trying to talk. Each episode lasted 20 to 30 seconds. Afterward the boy was his usual self and could tell his father what had been said to him.

The child has had no intercurrent illnesses or abnormal behavior apart from these "spells," and he has lost no abilities. A paternal cousin and grandfather had seizures during childhood but "grew out of them." The examination is completely normal.

Questions

1. What history would suggest that a child had a seizure?
2. How does the physician determine if a child has a seizure disorder (eg, epilepsy)?
3. How do electroencephalography and other tests help in classifying the type of seizure disorder?
4. How does the physician determine the best course of short- and/or long-term management?

Seizures are a common medical problem in children. Diagnosing an episode that does not contain generalized convulsing movements as a seizure is sometimes problematic, however. Seizure is an episodic, stereotypical behavior syndrome of abrupt onset with loss of voluntary control, resulting in loss of responsiveness and rarely provoked by external stimuli. Frequently, the occurrence of this behavior correlates with interictal brain electrical discharges on electroencephalography (EEG), and the behavioral ictus (ie, seizures) should match temporally with a period of electrical hypersynchrony if it occurs during the EEG recording.

A detailed history of the nature of the episodic behavior from an eyewitness or a video recording is paramount in making the diagnosis of a seizure disorder and elucidating the type of seizure problem. The EEG is most often an adjunct to diagnosis. It is abnormal in many individuals who do not have clinical seizures, and it may be normal interictally in many patients with clinical seizures because of its sampling limitations. Special techniques can sometimes help alleviate these limitations.

Epilepsy is a seizure problem that implies recurrence of seizures. Identifying the type of seizure problem is important in devising the management plan. Seizures can simply be classified as primary generalized seizures, that is, involving the whole cerebrum from the outset, or partial seizures. Some partial seizures can secondarily generalize, however, thereby clinically mimicking primary generalized seizures after their onset. Distinguishing these entities illustrates the importance of eyewitness information. Many treatment options are available, but the therapeutic plan must be individualized to the child's seizure type or clinical syndrome to optimize seizure control and minimize side effects. With appropriate treatment, most children with seizure disorders are not handicapped scholastically or socially and can enjoy normal lives.

Epidemiology

Fifty million people worldwide have epilepsy, with 3 to 4 million of those in the United States (1.2% of the US population). Approximately 0.5% to 1.0% of all children experience at least 1 afebrile seizure. In children younger than 18 years, the new onset epilepsy incidence rate per year is approximately 0.05%. Recurrent seizures can occur as a component of a static encephalopathy after brain malformation or dysgenesis, encephalitis or meningitis, metabolic disorder, hypoxic-ischemic injury, or severe head trauma. Such secondary or symptomatic seizures make up approximately one-third of childhood epilepsies. The remaining two-thirds of epileptic seizures occur presumably as part of a genetic epileptic syndrome. As genetic knowledge increases, eventually the specific cause or association of seizures in most children will be diagnosed.

Clinical Presentation

Children present with a history given by observers of an episode of abrupt onset characterized by a loss of ability to respond to external stimuli (Box 131.1). The child may experience various difficult-to-describe sensory, emotional, or psychic phenomena (ie, aura) before losing consciousness. Observers then see convulsive muscle activity, after which the patient may be sleepy. With some seizures, observers may note only an akinetic or staring spell; however, other seizures present with dramatic, rhythmic spasms of the face, extremities, or torso. Major motor seizures are frequently also associated with systemic autonomic changes, including changes in skin vascular supply causing color change, sweating, saliva production, and loss of sphincter control. Approximately 10% of children have a headache before or after their seizure. With the exception of the common provocative factors of fever, intercurrent illness, and sleep deprivation and the much rarer provocative factors of the reflex epilepsies, most seizure episodes are neither provoked nor attenuated by environmental factors. Between episodes, a child's general physical and neurologic examination may be entirely normal.

Pathophysiology

A seizure represents a sudden, synchronous depolarizing change in the electrical activity of a network of neurons that becomes widely propagated over the cortex, affecting awareness, responsiveness to external stimuli, and motor control. The propagation may be enhanced by defects in cell ion channels. Focal seizure disorders may result from a focal cortical lesion, such as a glial scar caused by a remote insult (eg, trauma, infarct), or a dysgenesis or primary cortical dysplasia that disrupts the electrical circuitry. The focal abnormality also could contain hamartomatous immature cells and abnormal synaptic properties and allow for periodic, abnormal transmission of impulses.

Exactly what initiates the change in dynamic between excitatory and inhibitory influences on the neuron, the synchronous depolarization of the neurons, and the widespread network propagation is not well understood, and a rigorous analysis of abnormal neuronal and cerebral neurophysiology is beyond the scope of this chapter. Several different physiologic mechanisms, including disrupted neuronal circuitry; voltage- and ligand-gated membrane ion channel abnormalities; abnormal excitatory or inhibitory neurotransmitter or receptor production, degradation, or uptake, including a critical protein interaction involving the γ-aminobutyric acid (GABA) type A α-2 subunit of its inhibitory receptor; and perhaps glial support mechanisms, could each be involved depending on the type of epilepsy or epilepsy syndrome. One example is familial childhood absence epilepsy, which results from abnormal thalamocortical circuitry that is in some way developmentally vulnerable. Another example is cryptogenic West syndrome (ie, infantile spasms), an "inter-neuronopathy" that has been associated with several genes, including *LIS1, DCX,* and *ARX* (sometimes resulting in agyria), which are important in GABAergic inhibitory interneuron development. A third example is the neuronal voltage-gated sodium channel subunit gene, *SCN1A*, which is mutated in the mild phenotype of "generalized epilepsy with febrile convulsions plus" and also mutated but in different regions of the gene sequence in the much worse phenotype of Dravet syndrome, which was previously known as severe myoclonic epilepsy of infancy. Neonates are more susceptible because of a paradoxical excitatory effect of GABA receptors in immature neurons, a relative abundance of *N*-methyl-D-aspartate receptors, and a peak in dendritic spines and synapse numbers. Further understanding of the mechanism involved in familial epilepsy syndromes awaits the definition of relevant genes, their expression and product functions, as well as the effects of changes in exon base pair sequence, regulatory regions of the genome, or epigenetic mechanisms on membrane polarization, synaptic function, and circuitry physiology.

Box 131.1. Diagnosis of Seizure in the Pediatric Patient

- Abrupt loss of responsiveness
- Rhythmic clonic movements
- Sustained changes in posture or tone
- Simple automatic movements
- Drooling or bubbles of saliva present on the lips
- Completely unresponsive
- Staring without change in tone or posture
- Simultaneous change in cerebral electrical activity (eg, repetitive discharges)

Seizure Types

Seizures can be simply classified by their ictal appearance as either primary generalized seizures, which include grand mal seizures, generalized tonic-clonic convulsions, and petit mal (absence) seizures (so named because of the child's complete loss of awareness at the outset of the episode), or focal (ie, localization-related) seizures, which include focal motor, psychomotor, and other partial disorders (Box 131.2). Epilepsy syndromes are also a useful means of

Box 131.2. Simplified Classification of Epileptic Seizures by Ictal Appearance

Partial Seizures (Seizures Beginning Locally)

- Elementary symptoms: focal seizures
- Complex symptoms: psychomotor seizures
- Partial seizures evolving secondarily to generalized seizures

Generalized Seizures (Bilaterally Symmetric; Onset not Local)

- Absence seizures (ie, petit mal): typical and atypical
- Tonic-clonic seizures
- Tonic seizures
- Myoclonic seizures (eg, minor motor)
- Atonic seizures (ie, drop attacks)
- Infantile spasms

Unclassified Seizures (Includes Neonatal "Subtle" Seizures)

classifying seizures by their clinical patterns (ie, diagnosis, therapy, and prognosis). Even with a known genetic cause, the same gene can produce more than 1 epileptic syndrome (Box 131.3). The examples presented here are not an exhaustive list of seizure syndromes; rather, they are among the more important types encountered in practice.

Box 131.3. Epilepsy Syndromes by Age of Onset

Neonatal

- Benign (idiopathic) neonatal seizures, historically termed "fifth day fits"
- Benign familial neonatal epilepsy
- Early infantile epileptic encephalopathy (eg, Ohtahara syndrome)
- Early myoclonic encephalopathy

Infantile

- Myoclonic epilepsy in infancy, which is a benign Dravet syndrome variant
- Benign epilepsy of infancy
- Benign familial infantile epilepsy
- Epilepsy of infancy with migrating focal seizures
- Hemiconvulsion-hemiplegia-epilepsy syndrome
- West syndrome (eg, infantile spasms, hypsarrhythmia; infantile spasms are to be distinguished from benign myoclonus of early infancy, which is not an epilepsy)
- Severe myoclonic epilepsy of infancy (as in classic Dravet syndrome)
- Myoclonic encephalopathies in nonprogressive disorders

Childhood

- Genetic epilepsy with febrile seizures plus (can begin in infancy)
- Panayiotopoulos syndrome (ie, early-onset benign childhood occipital epilepsy)
- Myoclonic-atonic (formerly astatic) epilepsy (ie, Doose syndrome)
- Benign epilepsy with centrotemporal spikes (ie, benign rolandic epilepsy)
- Late-onset childhood occipital epilepsy (ie, Gastaut type)
- Epilepsy with myoclonic absences (ie, Tassinari syndrome)
- Lennox-Gastaut syndrome
- Epileptic encephalopathy with continuous spike and waves during slow wave sleep
- Acquired epileptic aphasia (ie, Landau-Kleffner syndrome)
- Childhood absence epilepsy (ie, pyknolepsy)
- Generalized epilepsy with eyelid myoclonus (ie, Jeavons syndrome)

Adolescence to Adult

- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with generalized tonic-clonic seizures alone
- Progressive myoclonus epilepsy
- Mesial temporal lobe epilepsy with hippocampal sclerosis
- Autosomal dominant focal epilepsy with auditory features
- Autosomal dominant nocturnal frontal lobe epilepsy

Syndromes with Less Specific Age Relationship

- Familial focal epilepsy with variable foci (childhood to adult)
- Reflex epilepsy

Two-thirds of nonfebrile seizures in children result from a focal seizure disorder. *Psychomotor seizures* are focal seizures that usually are preceded by a sensory aura or sometimes emotional behavioral manifestations and have a wide range of ictal behaviors, including focal clonic jerking, aversive or asymmetric hypertonic posturing, and more complex stereotypic fumbling or fingering behaviors. Seizures may be followed by postictal confusion or drowsiness. In some instances, children have partial sensory awareness but are unable to respond during seizures. In other cases, however, they are completely unconscious. The initial partial motor manifestations may not be seen by the observer before the movements rapidly generalize. Partial seizures are more often associated with focal brain pathologic processes, including traumatic lesions, infarcts, malformations, infections (eg, viral encephalitis, cerebral cysticercosis), and hippocampal sclerosis. The latter is rare in children but has been associated with a distant history of a prolonged febrile seizure. A few of these etiologies may be found with a characteristic appearance on magnetic resonance (MR) imaging; however, in most cases the etiology and its location are not apparent on MR imaging alone and require a combination of techniques to find the source of the resistant seizures.

Benign epilepsy syndromes occur in children with normal developmental history, respond well to therapy, and remit without sequelae. Rolandic seizures, or benign epilepsy with central temporal spikes, is a relatively common partial seizure syndrome that sometimes is familial and has a good prognosis for resolving by adolescence. These episodes commonly occur when children are falling asleep, during sleep, or on awaking. Motor manifestations involve the tongue, mouth, or face but can sometimes generalize to the rest of the body. The clinical syndrome is accompanied by a characteristic focal EEG discharge over the central temporal region of the scalp. Other benign syndromes include benign familial infantile seizures; benign infantile seizures with mild gastroenteritis; childhood occipital epilepsy characterized by visual symptoms and EEG occipital spike-wave discharges; and Panayiotopoulos syndrome, which is characterized by paroxysmal autonomic dysfunctions such as vomiting and other gastrointestinal motility problems, pallor, mydriasis, and cardiorespiratory and thermoregulatory abnormalities (lasting up to 30 minutes), often ending in generalized convulsing and largely occurring in sleep.

An absence seizure may sometimes be difficult to distinguish from a partial seizure (Table 131.1). The absence spell is a brief (2–15 seconds) loss of consciousness without loss of tone. Staring into space and minor movements, such as lip smacking or semi-purposeful-appearing movements of the hands are often the only observed behaviors. There is no postictal period. Because absence seizures occur multiple times per day and children are often unaware of them, parents or guardians may dismiss the subtle behavior change as selective attention or daydreaming; however, these seizures may adversely affect learning and carry a risk of injury. Hyperventilation, a useful diagnostic test that can be performed in the office, may provoke absence seizures. The EEG is generally confirmatory and may also distinguish classic petit mal seizures with 3-per-second

Table 131.1. Partial Complex Versus Absence Seizures

Characteristic	*Partial Complex*	*Absence*
Aura	Frequent	None
Loss of consciousness	Sometimes partial	Complete
Motor movements	Sometimes complex	Blinking or none
Postictal state	Frequent	None
Duration	>30 seconds	<15 seconds
Frequency	A few per month to a few per day	Many per hour or day
Hyperventilation provoked	No	Yes
Findings on electroencephalography	Variably localized discharge or normal	3-per-second spike-wave generalized
Prognosis past adolescence	Frequently persists	Rarely occurs

spike-wave discharges from variant syndromes. The classic petit mal is more often familial with dominant inheritance, age-specific occurrence between 4 and 16 years as childhood or juvenile absence, and sensitivity to ethosuximide treatment, whereas the atypical variant has a poorer prognosis for early resolution and is more resistant to anticonvulsant therapy. Juvenile myoclonic epilepsy begins during adolescence, but even if symptoms abate, treatment is often necessary into adulthood and is characterized by upper extremity myoclonus (ie, dropping or flinging behaviors) and convulsive seizures in the morning.

Neonatal seizures may be tonic, focal clonic, or multifocal clonic. The seizure problem is less often primary, and a vigorous search for an etiology of the seizure is more often successful than with older children. Problems commonly resulting in neonatal seizures include hemorrhage (eg, germinal matrix hemorrhage in the preterm neonate, subarachnoid or subdural hemorrhage from birth trauma in older neonates); hypoxic-ischemic damage from asphyxia; infections producing postnatal sepsis or meningitis or prenatal encephalitis; drug withdrawal in the newborn exposed to illicit drugs in utero; metabolic problems, including hypoglycemia, hypocalcemia, or hypomagnesemia in the neonate of a diabetic mother; amino or organic acidopathies occurring a few days after feedings have begun; congenital brain malformations; and genetic syndromes, including benign neonatal familial epilepsy, benign familial infantile epilepsy, and pyridoxine-dependent epilepsy.

Several more malignant seizure syndromes exist that have onset at typical ages, perhaps related to more widespread maturational events in brain circuitry or ion channels. Although the appearance of the seizures within each of these syndromes is stereotypical and ultimately interictal cognition is commonly affected, resulting in their designation as an "epileptic encephalopathy," in fact a wide variety of etiologic diagnoses may produce these syndromes.

West syndrome is an age-related seizure syndrome that involves typical but sometimes subtle movements of flexion contraction of the trunk with the head bowed or sudden raising of the arms, sometimes accompanied by a cry. These behaviors, infantile spasms, occur stereotypically several times in succession in a series. This syndrome, which includes a characteristic EEG and a period of developmental arrest, occurs in infants and children between 3 and 24 months of age. Another, perhaps related, but rarer syndrome of frequent tonic spasms, *Ohtahara syndrome*, occurs during the neonatal period and is associated with tonic seizures, an abnormal neurologic examination, and often structural brain abnormalities. It is characterized by a different burst-suppression EEG pattern but carries a similar dismal prognosis for impaired intellectual development. *Dravet syndrome* arises out of typical febrile seizures that then occur without fever and subsequently manifest as staring spells and myoclonic seizures accompanied by delayed cognition. As many as 50% of these children may experience sudden unexplained death in epilepsy (SUDEP) by age 10 years. Landau-Kleffner syndrome involves loss of language abilities at age 3 to 5 years in the context of epileptic seizures and a very abnormal EEG pattern in sleep. It is related to continuous spike and waves during slow wave sleep, which is associated with a more general cognitive decline. A fifth syndrome in older children that is also associated with a different but characteristic EEG pattern, Lennox-Gastaut syndrome, has the same poor prognosis for seizure control and cognitive development but produces several different behavioral seizure types, including tonic, absence, and drop attacks. Different types of brain lesion in these age groups (including focal lesions) can result in the same generalized seizure syndromes. Examples include tuberous sclerosis; neonatal ischemia, hemorrhage, or meningitis; and major central nervous system malformations. Other epileptic encephalopathies include early myoclonic encephalopathy, malignant migrating partial seizures of infancy, Rasmussen encephalitis, and Doose syndrome.

Differential Diagnosis

Seizures are distinguished from nonepileptic paroxysmal disorders based on patient history. The circumstances of place and time as well as details about the symptoms and nature of the behavior are important pieces of data. Syncope may be misdiagnosed as a seizure. Unlike seizure, however, the syncopal episode is frequently situational. It occurs when children are in hot or stuffy environments; when they have been standing in 1 place for a long time, such as during a ceremony or physical education class; or when they see or experience a painful event, such as an injection or phlebotomy. Boys may experience micturition syncope standing in the bathroom shortly after arising in early morning. Syncope often is preceded by symptoms of light-headedness, nausea, tinnitus, and eventually a gradual darkening of vision, sometimes without total loss of auditory perception. Observers may note pale skin color and cool damp skin.

Breath-holding spells are characterized by apnea and loss of responsiveness accompanied by cyanosis or pallid skin color. Breath-holding spells are also situational. Infants or children are often upset or crying just before such spells. They may be frightened

by a seemingly minor injury or angry after a toy is taken away or they are disciplined. Children may then throw themselves backward and stiffen while closing their glottis in expiration, and they may even have a few clonic jerks after losing consciousness (see Chapter 52).

Selective attention is frequently mistaken for absence seizure. Selective attention often occurs when children are involved in relatively passive activities (eg, watching television, playing a video game, daydreaming) and do not respond to verbal stimuli, such as hearing their own name called. Generally, the attention lapses do not occur during talking or eating; seizures will occur, however, even during these activities.

Epileptic seizures must also be differentiated from pseudoseizures (ie, psychogenic nonepileptic seizures), which occur most often in patients who have true seizures. Such episodes may include ictal eye closure and pelvic thrusting but also may resemble true seizures accurately, the psychodynamics of secondary gain or other motivation for the behavior may not be readily apparent, and the "need" for attention may be legitimate. The finding that the standard EEG is normal does not exclude a true seizure and thus is not helpful. Pseudoseizures should be suspected in children who may have witnessed seizures in relatives or close friends, who have seizures that consistently recur in the same situations, whose seizure frequency is not decreased with therapeutic levels of anticonvulsants, and whose seizures appear suggestible. Often, diagnosis can be supported in complicated cases by simultaneous video EEG monitoring, which shows a lack of correlation of electrical abnormalities with the behavior in question. Immediate postictal serum prolactin level also may be normal, and psychological assessment may detect underlying emotional problems related to prior trauma (eg, sexual abuse, other major psychological trauma). The prognosis of pseudoseizures in children generally is better than in adults and relates to the more acute psychosocial genesis of the problem in most children.

Infants and older children have several behaviors that mimic seizures. Infantile gastroesophageal reflux (ie, Sandifer syndrome) may have the appearance of brief epileptic tonic spasms but has a consistent temporal relationship to feeding. Benign paroxysmal vertigo occurs in the infant or toddler and presages migraine later in childhood. *Infantile shuddering* consists of brief, rapid side-to-side shaking of the head and trunk. Older children can experience a paroxysmal dystonia, which is provoked externally and produces a change in truncal tone and posture and a brief cessation of movement. *Tics* are sudden, brief stereotypical movements preceded by an urge and are partially suppressible. *Stereotypies* are recurrent movements that are often self-stimulatory and frequently occur with severe autism. None of these entities produces a loss of responsiveness of the child.

Sleep myoclonus is a normal nonepileptic variant that is common in infants; however, in older children accurate diagnosis of paroxysmal events in sleep may be a challenge because the motor behaviors of nonrapid eye movement sleep or other parasomnias may mimic nocturnal frontal lobe epileptic seizures. Video EEG polysomnography is also helpful in distinguishing between frontal lobe epileptic seizures and nocturnal parasomnias, which are not associated with ictal discharges.

Evaluation

History

The history should determine the exact events surrounding the seizure episode. A detailed history of the nature of the behavior from an eyewitness is extremely important (Boxes 131.4 and 131.5). The observer can be asked to video record a subsequent event. The physician must determine whether the child experienced any loss of the child's normal level of responsiveness. Typically, this change in mental status is abrupt, although a warning behavior or aura that lasts for a few seconds may precede complete loss of responsiveness. The warning behavior or aura for a seizure may be a cry, an expression

Box 131.4. Initial Evaluation of Seizure Patients

- Eyewitness account of the episode and/or video recording
- Description of the child's own experiences before, during, and after the episode if the child is sufficiently articulate
- History from caregiver concerning remote injuries to the nervous system, progressive neurologic symptoms, or intercurrent illness
- Careful neurologic examination for signs of cerebral hemisphere lateralization
- Brain magnetic resonance imaging, particularly for the patient in whom a partial seizure is observed, a crescendo history of neurologic symptoms is obtained, focal neurologic signs are noted on interictal examination, or postictal encephalopathy persists too long
- Waking and sleep electroencephalography with hyperventilation (if the patient can cooperate)

Box 131.5. What to Ask

Seizures

- Where was the child, and what was the child doing when the episode began?
- Did the child experience a loss of responsiveness?
- Did the child show any warning behavior or aura (eg, a cry, a facial expression of fear, irritability)?
- Did any part of the child's body become stiff? Was any shaking or jerking apparent?
- What did the child's eyes do, and was saliva produced at the mouth?
- Did the child's skin change color?
- Did the child experience a loss of sphincter control?
- How long did the episode last?
- Has the child been well recently?
- Did the child have a complicated birth, head trauma, meningitis, or other previous brain damage?
- Have episodes of a similar nature occurred previously? If so, when did they begin and how frequently do they occur?
- Has the child's development and school experience progressed normally?
- Does the child have any relatives who have had seizures?

of fear or anxiety, or nonspecific irritability. The child who is articulate may be able to describe a discrete sensory phenomenon or relate a less distinct or even indescribable sensation.

A change in muscle tone and activity is frequently associated with the abrupt change in mental status, unless the spell is an absence seizure. Most often, the tone is increased with general extensor posturing, more focal hypertonicity, or more complex torsion or aversive upper-body posturing. The patient may fall if not supported. Rhythmic jerking or clonic movements (focal or general), including the trunk, limbs, face, and eyes, may occur concomitantly. Respirations may involve gagging sounds, rhythmic grunting, or silent, nearly imperceptible movements. Swallowing may not occur, so that saliva pools or forms bubbles at the lips. Autonomic changes, including skin color change (ie, circumoral cyanosis), increased pulse, and loss of sphincter control, frequently occur with major motor spells. The ictal period generally lasts 30 to 120 seconds, although observers frequently overestimate this time. Postictal periods of sleepiness or lethargy may occur. The length of these periods often is correlated with the length or intensity of the seizure.

Children and those around them are sometimes unaware of the occurrence of absence seizures. Often, an observant teacher brings the child's problem to a physician's attention. During a spell, a child has no change in tone or clonic movements and may have only subtle facial or hand movements. The episode lasts only a few seconds, and there are no preictal or postictal behaviors.

Historical information can also help determine potential etiologies of the seizure problem. A known distant brain insult or a hereditary disposition or consanguinity may be related to the cause. The patient with progressive loss of skills should be evaluated for a degenerative disease. Many degenerative conditions can masquerade as epilepsy, and the physician must be continuously aware of progressive loss of vision, hearing, coordination, strength, or cognition as clues to initiate a more comprehensive workup.

Physical Examination

Children should be examined carefully for focal neurologic signs, particularly cerebral hemisphere-related asymmetries in strength, tone, or tendon reflexes. The examination should include a developmental assessment and mental status examination. The physician should evaluate for signs of potential genetic problems, such as dysmorphic features, microcephaly, or organ malformations, which often correlate with cerebral dysgenesis; abnormal skin pigmentation or vessels, which are suggestive of a neurocutaneous disorder; and organomegaly or bony abnormalities, which may be indicative of a storage disorder. A careful eye examination or ophthalmologic consultation might also reveal evidence of a neurocutaneous, neurodegenerative, or dysgenic disorder. The child who is old enough to cooperate should be asked to hyperventilate, which might provoke an absence spell if the history is suggestive of this type of seizure.

Laboratory Tests

An EEG should be requested to aid in the diagnosis of the type of seizure disorder, although the diagnosis should not rest on the EEG alone. In the child with partial seizure disorder, the interictal discharge is helpful in localizing the initial site of abnormal electrical activity. A sleep record is often essential for observing the most useful abnormalities; 40% of children with epilepsy have a normal EEG. If a normal waking EEG is obtained and seizures continue to recur, it is sometimes useful to help promote sleep during the recording by prior sleep deprivation carried out by the parents or caregivers. Patient anxiety about the test and setting as well as the discomfort of all the wires may make sleep elusive even after sleep deprivation. Special techniques (eg, prolonged monitoring with telemetry, special anatomic electrode placements) can sometimes help overcome the standard EEG limitations of sample time and inaccessible areas of cerebral cortex. It should be noted, however, that even the standard EEG is rarely normal in petit mal disorders.

Historical information can frequently guide the need for metabolic tests. A blood sugar determination should be done acutely; however, electrolytes are rarely abnormal in older children who have been well prior to the seizure. Urine toxicology should be done in a teenager with possible illicit drug use. Neonates and infants with recurrent unexplained seizures should undergo metabolic screening, including urine organic acid and amino acid levels, ammonia level, and acyl and free carnitine levels. If seizures persist, with resulting mental status changes, the physician should consider screening for cerebrospinal fluid glucose, lactate, and amino acid levels; conducting lysosomal and peroxisomal screening; and a diagnostic or therapeutic trial of pyridoxine. Tissue biopsy histologic analysis and specific assays may be indicated when physical signs are suggestive of possible storage or other metabolic etiologies. Dysmorphic features may indicate the need for chromosome analysis, a gene copy number variant screening array, or exome sequencing unless together they suggest the need for a specific diagnostic gene test. Epilepsy gene panels are available to assess for genes associated with epilepsy.

Imaging Studies

Magnetic resonance imaging is particularly helpful if a progression in neurologic symptoms or signs has occurred, the patient has a history of prior neurologic insult, an asymmetry of strength or tone is noted on examination, or signs of dysgenesis are present in other parts of the body. Even in the absence of these factors, partial or focal seizures have a higher yield of abnormal imaging results than do febrile seizures or petit mal disorders, which have a low yield. Finding a structural abnormality can obviate the need for expensive metabolic testing and can help narrow gene testing. In the acute period, intravenous contrast should generally be given because the cause of the seizure may be indicated by the loss of focal blood-brain barrier with an inflammatory or neoplastic lesion. The child with recurrent or resistant focal seizures should undergo MR imaging, particularly when surgical treatment is under consideration. Coronal MR imaging can detect mesial temporal sclerosis, a lesion in the hippocampus that occurs in chronic temporal lobe epilepsy, and 20% of children with this finding will have had febrile seizures. Helpful additional modalities in studying surgical candidates in a phased evaluation program include ictal positron emission tomography using fludeoxyglucose F 18, interictal positron emission tomography using α-methyl-L-tryptophan, single-photon emission computed tomography, functional

MR imaging, magnetoencephalography, and electrocorticography after craniotomy. These studies help define the nature of damaged or epileptic cortex and differentiate it from normal cortex.

Management

When an episode of abrupt loss of consciousness or tone with a potential for recurrence has occurred, families must be cautioned about the risks of drowning, falls from high places, burns, and accidents with operating machinery, including motorized vehicles.

Anticonvulsants are the mainstay of management of seizure disorders (Table 131.2). However, the physician must realize that both seizures and antiepileptic drugs affect brain development and could have long-term consequences, such as altered cognition. This observation may be especially true in the case of neonatal seizures, in which the seizures themselves may contribute to adverse outcomes and the standard treatment of phenobarbital has been shown in some long-term studies to inhibit learning. One-half of first-time seizures in otherwise neurologically normal children do not recur.

Table 131.2. Drugs Useful for Managing Seizures

Seizure Type	*Anticonvulsant*	*Dose*	*Toxic Symptoms/Side Effects*
Focal (narrow spectrum)	Carbamazepine	Approximately 15 mg/kg/day	Gastrointestinal distress, headache
	Phenytoin	4–8 mg/kg/day	Ataxia, nystagmus, bone changes
	Primidone	12–25 mg/kg/day	Drowsiness, ataxia
	Oxcarbazepine	30 mg/kg/day	Drowsiness, rare sodium depletion
	Lamotrigine	4–7 mg/kg/day	Dizziness, sedation, rash (eg, Stevens-Johnson syndrome)
	Gabapentin	4–8 mg/kg/day	Somnolence, ataxia
	Vigabatrin	15–50 mg/kg/day	Drowsiness, visual field defects
	Zonisamide	4–6 mg/kg/day	Sedation, metabolic acidosis
	Levetiracetam	10–60 mg/kg/day	Behavior or personality change
	Rufinamide	10–45 mg/kg/day	Sedation, headache
	Lacosamide	1.5–6 mg/kg/day	Dizziness, ataxia, caution with cardiac disease
Neonatal	Phenobarbital	5–6 mg/kg/day	Lethargy, irritability, osteopenia
	Topiramate	6–10 mg/kg/day	Sedation
	Levetiracetam	10–60 mg/kg/day	Sedation
	Pyridoxine	5–10 mg/kg/day divided 3 times a day for at least 3 days	None
Generalized (broad spectrum)	Valproic acid	20–60 mg/kg/day	Tremors, hair loss, thrombocytopenia, weight gain, pancreatitis
	Felbamate	45 mg/kg/day	Insomnia, anorexia, bone marrow aplasia
	Lamotrigine	4–7 mg/kg/day	Dizziness, sedation, rash (eg, Stevens-Johnson syndrome)
	Zonisamide	4–6 mg/kg/day	Sedation, metabolic acidosis
	Levitiracetam	10–60 mg/kg/day	Behavior or personality change
	Rufinamide	10–45 mg/kg/day	Sedation, headache
	Topiramate	6–10 mg/kg/day	Weight loss, sedation, speech disturbance, metabolic acidosis
	Clorazepate dipotassium	0.3–1.5 mg/kg/day	Drowsiness
	Clonazepam	0.01–0.2 mg/kg/day	Drowsiness, ataxia
	Clobazam	0.15–0.5 mg/kg/day	Drowsiness
	Perampanel	0.05–0.2 mg/kg/day	Weight gain, fatigue, nausea, rarely hostility or aggression
Absence	Ethosuximide	30 mg/kg/day	Nausea, hiccups
	Valproic acid	20–60 mg/kg/day	Tremors, hair loss, thrombocytopenia, weight gain
Infantile spasms	Adrenocorticotropic hormone	40 units/m^2/day	Increased appetite, irritability, acne, immunosuppression
	Prednisolone	0.14–2 mg/kg/day or 40–60 mg/day	Increased appetite, irritability, acne, immunosuppression
	Valproic acid	20–60 mg/kg/day	Tremors, hair loss, thrombocytopenia, weight gain
	Vigabatrin	15–50 mg/kg/day	Drowsiness, visual field defects

Anticonvulsants are prescribed based on seizure classification and individual factors. Consideration is given to the risk of recurrence of seizures, particularly prolonged seizures and the physical danger of recurrence. The social stigma of having a seizure at school is significant and outweighs the potential medication side effects. A known structural lesion on imaging or physiologic lesion demonstrated on EEG may also be suggestive of a higher risk for recurrence. The choice of anticonvulsant depends on age, sex, neurologic diagnosis, seizure type or epilepsy syndrome, other conditions or medications, and social factors. The doses and combination of anticonvulsants prescribed for children also depend on a balance of seizure resistance, risk of recurrence, and potential toxicity of medication. The initial goal in an otherwise neurologically intact child might be complete control with a single medication and the minimum toxicity possible. When this goal is not achieved, doses are advanced to an individualized optimal balance of seizure control and tolerated toxicity. In a very disabled nonambulatory child, a goal might be to prevent status epilepticus but tolerate some brief seizures to have reduced medication toxicity.

Levetiracetam has a broad spectrum of efficacy in seizure types, wide dosing range, intravenous availability, and little organ toxicity or interaction with other medications; however, it can cause mild irritable personality changes. Oxcarbazepine and carbamazepine are often recommended for focal seizures. Toxicity of these is generally mild, but adverse events can include gastrointestinal upset, dizziness, and headache. Carbamazepine can cause a flushing syndrome in Asian populations and has been known to aggravate idiopathic generalized and myoclonic epilepsies, including Lennox-Gastaut syndrome, however. Phenytoin is also effective for partial seizure types and can be given intravenously for status epilepticus, but it can worsen absence seizures. Phenobarbital is effective in neonatal seizures but may have deleterious effects on behavior and learning in older children. Pyridoxine, folinic acid, and pyridoxal 5′-phosphate may be successful in resistant neonatal seizures because of cofactor dependencies. Ethosuximide is used for petit mal seizures. Valproic acid is used for more common atypical petit mal seizures but is broadly effective in other seizure disorders that are resistant to other anticonvulsants because it works by several mechanisms. It should be used with caution in females who might conceive because of an increased risk of fetal neural tube defects and offspring learning disabilities and used with caution in infants younger than 2 years who are at higher risk of metabolic disorders. Felbamate is also effective in many epilepsy syndromes that are difficult to manage, although its use has been limited because of the quite small but nevertheless frightening incidence of irreversible severe bone marrow suppression and liver toxicity. Other anticonvulsants, including lamotrigine, vigabatrin, topiramate, lacosamide, zonisamide, rufinamide, clonazepam, clorazepate dipotassium, clobazam, and gabapentin have proven effective. Lamotrigine is useful in partial and primary generalized seizure disorders but may worsen seizures in patients with Dravet syndrome and reduces hormonal birth control efficacy. All sodium channel blocking agents as well as vigabatrin and tiagabine hydrochloride should be avoided in patients with Dravet syndrome. Vigabatrin is useful for managing infantile spasms caused by tuberous sclerosis. Topiramate is effective in the management of partial seizures, generalized seizures, and Lennox-Gastaut syndrome. Rufinamide and clobazam are particularly effective in patients with Lennox-Gastaut syndrome. Cannabidiol has shown promise for use in patients with Dravet and Lennox-Gastaut syndromes. Zonisamide is effective in the management of partial and generalized seizure disorders, and lacosamide is effective in the management of partial seizure disorders. Lacosamide may be used intravenously as well. Clonazepam, clorazepate dipotassium, and clobazam are adjunctive benzodiazepines that are effective in the management of several seizure types. Gabapentin can be useful as an adjunctive agent because of its lack of interaction with other anticonvulsants. Rectal diazepam, a universal antidote for status epilepticus, empowers the family to begin treatment at home before paramedic arrival for a long (>5 minutes) seizure or cluster of seizures.

Periodic monitoring of efficacy and side effects is essential in children who take medication daily on a long-term basis. A log of seizure frequency helps assess medication efficacy. Neurologic symptoms such as sedation and ataxia are the most common side effects, but many others are possible. The perception of symptoms being related to the medication as well as the actual presence of side effects or toxicity contribute to the complex issue of compliance. Serum drug levels are available for some medications and are useful in monitoring compliance, dosage, and the likelihood that symptoms are the result of drug side effects. Compliance is improved if a medication formulation with less frequent dosing can be used. Organ toxicity (ie, bone mineralization, bone marrow blood cell production, liver function, pancreas function) must be considered and monitored with many medications, although routine laboratory testing after a few months on stable doses is rarely necessary. Hypersensitivity reactions and Stevens-Johnson syndrome usually occur within 2 months of beginning the medication. Ethnic variability in drug metabolism and drug interactions can be important and involve the liver cytochrome P-450 system. This variability of the liver cytochrome P-450 system effect includes inducing potential of barbiturates, inhibiting potential of other medications such as erythromycin, and inhibiting detoxification systems that involve carbamazepine metabolism, resulting in acutely high levels and clinical toxicity. New educational problems in a child with epilepsy deserve aggressive evaluation to determine a common etiology of the underlying seizure condition and alternatively for assessing medication toxicity or long-term detrimental effects.

Nonpharmacologic therapeutic options are available for managing refractory epilepsy. Use of the ketogenic diet or the less intense modified Atkins diet has demonstrated success in approximately 50% of cases but requires considerable dietetic knowledge and family commitment. The vagal nerve stimulator delivers a regular electrical stimulus afferently to the central nervous system and allows for an abortive intervention by the caregiver with an external magnet. It is effective in approximately 50% of cases, enabling use of less medication in those patients and allowing a better overall quality of

life. Consideration of intracranial resection is warranted in select patients with epilepsy in childhood. Children with hemispheric seizure-associated syndromes, including Sturge-Weber syndrome, Rasmussen encephalitis, hemimegalencephaly, perinatal hemispheric infarction, catastrophic seizure disorders of early childhood (eg, infantile spasms related to a localized zone of epileptogenic cerebral tissue), and hamartomatous cortex-producing seizures, have benefitted the most often from surgical resection, but patients with refractory partial seizure disorders, including temporal lobe epilepsy, may also be candidates for such treatment. Extensive staged preoperative imaging and physiologic monitoring are necessary for these patients.

With the possible exception of rock climbing, sports participation is generally allowed for children with epilepsy. Swimmers must have individual supervision. Extra supervision is necessary around hot appliances and cooking equipment. Showers are preferable to baths. Attention-deficit/hyperactivity disorder is common in children with epilepsy, and the use of concomitant therapy, including stimulants, should be considered. Because of frequent behavioral and learning disability comorbidities, as well as social stigmatization, patients and their families often benefit from psychological and social therapy as well as support groups. Managing epilepsy often requires much more than just treating seizures.

Prognosis

Approximately two-thirds of children with a tendency for seizure recurrence have a good prognosis for prevention of further recurrence and few or no problems with side effects of medication. They can lead normal lives without handicap. Some of the seizure syndromes with a familial tendency, such as rolandic seizures and typical petit mal seizures, have a good prognosis for control by medication and complete resolution by the teenage years. The etiologic diagnosis is the most important prognostic factor. The type of epilepsy, EEG findings, child's age, difficulty of initial seizure control, and time since the last seizure are also important factors. Compared to seizure syndromes with a familial tendency and typical petit mal seizures, partial complex disorders sometimes have a poorer prognosis for early resolution and may be more resistant to treatment with anticonvulsants. Some seizure types have intrinsically poor prognoses. For example, infantile spasms are prognostically ominous because even in the absence of a metabolic diagnosis, children frequently suffer temporary brain growth and developmental arrest unless the seizures are controlled with medication. Approximately 10% to 25% of children, most often those with generalized symptomatic types of epilepsy, frequent seizures, high anticonvulsant use, and early onset of epilepsy, exhibit some intellectual decline. A small percentage of these patients develop an epileptic encephalopathy and are significantly handicapped. Children with seizures that are resistant to 2 concomitant medications have a much lower chance of responding to a third medication or other drug combinations. Regardless of age, 36% of patients fully respond to the initial antiepileptic drug, 22% respond to the addition of a second drug, only 3% respond to a third drug, and 38% become multidrug resistant. By parental report, 80% of children with active or uncontrolled epilepsy are restricted in their activities because of concern about a seizure occurring during the activity (eg, swimming). These children also are at increased risk for death, with an annual risk of 0.84% (of which 30% are the result of SUDEP), particularly if they have secondary epilepsy.

The individualized decision of when to discontinue medication after successful treatment is often complex. Generally, withdrawal of medications should be considered in most children after 2 years of seizure freedom. The prognosis for recurrence of seizures, parental/caregiver and children's reactions to seizures and the prospect of their recurrence, and social factors (eg, school participation) may all contribute to the decision. In older adolescents, it may be necessary to consider discontinuing driving for a time if medication is to be stopped. Children and parents/caregivers must be aware that none of the prognostic factors, whether considered individually or in combination, is an absolute predictor of seizure recurrence or nonrecurrence in a given child.

CASE RESOLUTION

On evaluation at the emergency department, the seizure was deemed to be a generalized seizure. The previous episodes recalled by the father have characteristics of partial seizures. The tonic-clonic seizure was likely a secondary generalized rather than a primary generalized seizure. The possibility of rolandic seizures is suggested by the circumstances of the prior episodes, drowsiness, facial or oral symptomatology, and family history. This diagnosis was confirmed on EEG. Oxcarbazepine was prescribed. The boy experienced no side effects or seizure recurrences and was able to successfully discontinue the medication 3 years later.

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CHAPTER 132

Autism Spectrum Disorder

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CASE STUDY

The mother of 18-month-old twin boys is concerned because 1 twin is not talking as much as his twin sibling. Both twins are quite active. The mother feels that even though the child is quiet, he is very smart. He likes to figure out how things work. He seems very sensitive to sounds and covers his ears around loud noises. He loves music and even knows which CD his favorite song is on. He will interact with his sibling but does not seem interested in other children.

During the office visit, both boys are quite active. It is difficult to perform an adequate examination because the twin with limited language is crying the entire time. He does not seem to seek out his mother for comfort. Although both children have stranger anxiety, the twin about whom the mother is concerned seems to have extreme stranger anxiety. He appears well otherwise.

Questions

1. What is autism spectrum disorder?
2. How does autism spectrum disorder differ from language delay?
3. How does the physician evaluate a child for autism spectrum disorder?
4. Where can a physician refer a patient with autism spectrum disorder?
5. What types of treatment are available?
6. Should a child suspected of having autism spectrum disorder receive further immunizations?

Autism spectrum disorder (ASD) is characterized by impairments in social communication as well as restrictive, repetitive, and stereotypic behaviors or interests. According to the *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (*DSM-5*), a person with ASD must display persistent communication, interaction, and behavioral challenges across multiple contexts. These disturbances must be present early on but may not be apparent until social demand exceeds the limitation. These characteristics must cause significant impairment and cannot be caused by cognitive impairment (Box 132.1). Cognitive impairment is often a comorbidity, however.

This new term, ASD, includes the previous terminology of autistic disorder, Asperger syndrome, and pervasive developmental disorder–not otherwise specified; the term ASD no longer includes Rett syndrome. Although criteria differ somewhat, all these disorders had in common an impairment in social communication and repetitive or unusual interests of varying degrees. These disorders require similar management and treatment, and assessing the level of impairment is somewhat subjective. Therefore, a single term—ASD—best incorporates all those individuals who are significantly affected by its symptomatology.

Box 132.1. Diagnostic Criteria for Autism Spectrum Disorder

- Deficits in social communication and interactions
  - — Social-emotional reciprocity
  - — Nonverbal communication
  - — Developing, maintaining, and understanding relationships
- Preferred patterns of behavior, interests, or activities
  - — Repetitive, stereotypic motor movements, use of objects, or speech
  - — Need for sameness, routines, and patterns of verbal or nonverbal behavior
  - — Fixated interests of abnormal intensity or focus
  - — Increased or decreased reactivity to sensory input or sensory aspects of the environment

Derived from *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.

Epidemiology

As recently as 1999, the prevalence of ASD was thought to be 1 in 2,500. More recent numbers from the Centers for Disease Control and Prevention published in 2014 cite a prevalence of 1 in 59 children in the United States. The prevalence in Europe, Asia, and North America averages between 1% and 2% of the overall population. Boys are affected approximately 4 times as often as girls, which equates to 1 in every 38 boys. Affected girls are often more impaired than boys, however. Autism is considered the fastest-growing developmental disability. This increase is, in part, the result of an understanding of a broader phenotype.

Clinical Presentation

Autism spectrum disorder is truly a spectrum of social communication deficits. Although a certain set of behaviors defines the disorder, any child may have any combination of the symptoms that result in the same outcome—severe and incapacitating social deficits. Furthermore, the challenges experienced by this population are more than just developmental delays; the behaviors of these individuals are aberrant and odd.

Many children with an ASD have difficulty with eye contact and body posture. Even those who have some eye contact often do not use their eyes to convey a social message. They may look out of the corner of their eyes, focus only on the lips of the speaker, or look only infrequently. In other words, they may make eye contact but at the wrong time. They may talk to others with their bodies facing away from them. They may not gesture to help clarify intention.

Whereas some children have limited communication, some offer too much information. They may be quick to talk to others about things they are interested in but be unable to talk to their conversational partner about that person's own interests. They seem socially insensitive. As younger children, they are often entertained by their own interests for long periods. Some have limited need for relationships, but others desire interaction but do not understand how to initiate or maintain interactions. Although some of these children are nonverbal, some repeat or echo what they hear from movies, television, or nearby conversation. Others seem able to converse but have trouble with social banter. It is important not to be deceived by a child who interacts with others or even gives hugs but only on the child's own terms.

Children with ASD often have a fascination with patterns. The pattern may be in the form of household routines or within a particular subject area. This may manifest in an obsession for sameness and resistance to change or an obsessive need to know everything about a certain topic. Many know all there is to know about such favorite topics as Thomas the Tank Engine or dinosaurs from the Jurassic Period but cannot answer a question such as, "How are you?" or "What is your name?" They may be upset by a road detour or a furniture rearrangement. Some of these children, because of an incredible ability to recognize patterns, can read as early as 2 years of age, even though they can neither speak functionally nor comprehend what they read.

A significant portion of children have difficulty with sensory processing. This takes the form of problems with smells, tastes, sounds, sights, and touch. This symptom may be manifest in the need to taste everything, including nonfood items; covering ears in loud situations; or an inability to tolerate tags in clothing.

A huge variation exists in cognitive ability. The severity of ASD is independent of cognitive ability. Although approximately 25% of those with ASD have intellectual disabilities, many are of normal intelligence and some are gifted.

Parents or caregivers often raise behavioral concerns. It is important to recognize red flags and behaviors that demand further evaluation (Boxes 132.2 and 132.3). That is, certain classic symptoms exist, but the physician must be mindful of the child who is simply unable to connect with others. Physicians should rely on their own instincts. Inconsistent symptoms are the hallmark of this disorder. Some parents or guardians of children with an ASD describe a phenomenon whereby the children are developing normally until 12 to 15 months of age and then suddenly lose skills or stop progressing. This finding is particularly concerning.

Box 132.2. Common Aberrant Behaviors Associated With Autism Spectrum Disorder (ie, Red Flags)

- Decreased eye contact (common but *not* universal)
- Only wants to be cuddled on the child's terms
- Areas of unusual knowledge—recognizes entire alphabet by 2 years of age, all types of dinosaurs by 4 years, names of all Thomas trains, interest in fans or spinning items
- More interested in how things work than with playing
- Unusual sensitivities—oversensitive to hearing, bright lights, shirt tags, new foods, new places
- Smelling or licking nonfood items
- Repeating words instead of answering questions, or answering off topic
- Difficulty interacting with other children
- Plays amongst children, not with them
- Resistance to change, "very independent"
- "In his/her/their own world"
- Lines things up
- Unusual hand movements or jumping when emotional
- Things have to be a certain way
- Odd tone of voice (ie, prosody)
- Increased pain tolerance

Box 132.3. Indications for Referral for Evaluation

- 12 months of age: Not babbling or gesturing (pointing, waving)
- 16 months of age: No single words
- 24 months of age: Absence of 2-word phrases
- Loss of language or social skills at any age

Derived from Filipek PA, Accardo PJ, Baranek GT, et al. The screening and diagnosis of autism spectrum disorders. *J Autism Dev Disord.* 1999;29(6):439–484.

Pathophysiology

Numerous proposed etiologic possibilities for the origins of ASD exist, from the inbreeding of computer "whizzes" to exposure to microwaves. However, no consistent explanation or pattern has emerged. It is known that the structure of the brain is different, but the reason why remains unknown.

Up to 10% of those with ASD have another medical condition that might have led to this disorder (Box 132.4). This leaves 90% of patients without an etiology, however.

Genetics seem to play an important role in the development of ASD. A risk of the disorder among siblings of up to 20% has been reported, which is more than 10 times the risk in the normal population. Family members are more likely to exhibit social deficits, anxiety, or depression than are family members who do not have a relative with the disorder. Several candidate chromosomes have been suggested as being associated with this disorder, but no 1 locus is responsible for this disorder.

It is also important to realize that up to 30% of children with ASD have abnormalities on electroencephalography (EEG). This finding may point to the structural abnormalities in an autistic brain but does not seem to account for the disease itself. The epileptiform changes should be evaluated by a neurologist to determine if

Box 132.4. Medical Conditions Associated With Autism Spectrum Disorder

- Epilepsy
- Fragile X syndrome
- Tuberous sclerosis
- Prader-Willi syndrome
- Visual or auditory impairment syndrome
- Down syndrome (ie, trisomy 21)
- Cerebral palsy
- Neurofibromatosis
- Congenital rubella

medication is indicated. Without an outward expression of seizures, however, many patients do not opt for treatment.

Several environmental markers have also been suggested as being linked to ASD, but most have not proved credible. Major epidemiologic studies within the United States and internationally have examined the roles of vaccinations, diet, and thimerosal preservative in the development of this disorder. None of these studies has found proof to support these theories. Known associations include older paternal age, preterm birth, and jaundice. Several studies have suggested that pollution may play an epigenetic role.

Much of the newer research suggests a fundamental neurobiologic difference in the prefrontal cortex, which likely occurs as the result of abnormal neuronal overgrowth in the first 20 weeks of gestation. This suggests a genetic or epigenetic etiology before birth in 90% of patients with autism.

Children with ASD should undergo routine health maintenance, including all recommended immunizations. No evidence exists linking ASD with immunizations.

Differential Diagnosis

Few entities present with impairment in the same 2 domains as those that are affected by ASD. A limited number of disorders mimic ASD (Box 132.5). However, several disorders exist that commonly occur with ASD that, if not identified, make treatment more difficult (Box 132.6).

Box 132.5. Disorders That May Mimic Autism Spectrum Disorder

- Hearing impairment
- Global developmental delay
- Tourette syndrome and comorbidities
- Selective mutism
- Reactive attachment disorder
- Lead ingestion
- Sensorimotor integration dysfunction
- Severe auditory processing/language deficit
- Severe anxiety
- Severe attention-deficit/hyperactivity disorder
- Brain trauma
- Childhood-onset schizophrenia

Box 132.6. Disorders That Can Occur With Autism Spectrum Disorder

- Tuberous sclerosis
- Congenital blindness
- Global developmental delay
- Chromosomal abnormalities (eg, Down syndrome, fragile X syndrome, Prader-Willi syndrome)
- Phenylketonuria
- Epilepsy
- Elevated lead level
- Congenital infections
- Brain trauma
- Bipolar disorder
- Neurofibromatosis
- Congenital profound hearing loss
- Tourette syndrome
- Landau-Kleffner syndrome
- Inborn errors of metabolism
- Anemia
- In utero exposure to drugs and/or alcohol
- Depression and/or anxiety
- Attention-deficit/hyperactivity disorder

Evaluation

No single diagnostic test, blood or otherwise, can confirm the diagnosis of ASD. Diagnosis is based on history, interaction with the child, and meeting *DSM-5* criteria.

History

Regular developmental surveillance and screening should be part of every well-child evaluation, especially between ages 9 and 30 months. In 2019, the American Academy of Pediatrics recommended that pediatricians conduct developmental and behavioral surveillance during all well child visits, developmental screening at the 9-, 18-, and 30-month visits, and standardized screenings of patients for ASD at 18 and 24 month. Special attention should be given to a child who has a sibling with ASD or a child whose parent or caregiver has expressed concern. Several standardized screening tools can be used, including the Parents' Evaluation of Developmental Status or the Ages and Stages Questionnaire, to identify developmental and social competency skills and concerns. The Modified Checklist for Autism in Toddlers, Revised, with Follow-Up (M-CHAT-R/F) is an excellent autism-specific screening tool with moderate sensitivity and high specificity for use at the 18- and 24-month visits to identify individuals at high risk for ASD. A positive M-CHAT-R/F screening is associated with ASD in 50% of patients and with developmental delay in 90% of patients. These screening tools are quick and easy and can be completed by the parent or caregiver in the waiting area or with minor assistance from office personnel.

For the child with suspected developmental difference, the physician must gather as much information as possible. Thorough birth and medical histories are important in helping to understand if early experiences may have predisposed the child to any deficits. For example, children born preterm are at increased risk for ASD. Monozygotic and dizygotic twins have high concordance. Older fathers or infertility treatments may have a role as well.

Family history is also important, because ASD is presumed to have a genetic contribution and it may be helpful in identifying other etiologies. Understanding family structure is helpful in determining whether abuse, neglect, or maternal depression play a role in the child's delay. It is important to remember, however, that ASD is not caused by poor parenting.

Developmental history is a critically important part of the history. The physician must probe all 4 areas of development: fine motor, gross motor, language, and social development (see Chapter 32). As stated previously, it is expected that the most significant delays will be in language and social interaction; however, delays may be noted in all components of development. Additionally, probing for abnormal behaviors specific to ASD helps distinguish this disorder from others. Box 132.7 contains some suggestions that may help elicit information relevant to a diagnosis of ASD in a toddler; the history should be adjusted based on the age of the child. The physician should always include early language milestones. Children with ASD tend to have *splinter skills*, that is, skills that may be normal or above developmental level for age. The physician should not let these skills distract from probing areas of suspected delay.

Finally, parents/caregivers and physicians often fall victim to common myths and excuses about development because it is not easy for many parents to discuss or admit delays (Box 132.8). These myths, although they may seem plausible, are not substantiated and only serve to further delay onset of intervention.

Physical Examination

A thorough physical examination with special attention directed to the growth parameters, neurologic examination, dysmorphic features, and neurocutaneous stigmata are essential to a complete evaluation. Height, weight, and head circumference should be plotted. Twenty-five percent of children with ASD have a head circumference greater than the 97th percentile. That is not to say that everyone with a large head has ASD, only that it is an associated feature. In utero infections may predispose to a small occipitofrontal circumference, but both a large and a small head circumference have developmental implications for ASD.

Detecting subtle physical signs, such as clinodactyly, simian crease, or a high-arched palate, although not diagnostic, is somewhat helpful in raising suspicion for neurodevelopmental delays. A Wood lamp evaluation may be helpful in uncovering neurocutaneous stigmata.

A series of dysmorphic features, such as a thin upper lip, flat philtrum, and upturned nose, may be suggestive of a syndrome, such as fetal alcohol syndrome. Hypotonia is a common finding among children with ASD but may be suggestive of an inborn error of metabolism. The physician must also check reflexes, because degenerative

Box 132.7. What to Ask

Autism Spectrum Disorder

Questions to Ask Parents/Caregivers

- Does your child seem to hear you? Did your child undergo a hearing test in the neonatal period?
- Does your child make noises? If so, what kind?
- When did your child say his, her, or their first word after "mama" and/or "dada"? Does your child have 2-word phrases?
- Are there any other behaviors that concern you?
- Can your child scribble? Has your child lost any skills? Does your child line things up?
- When did your child first walk? What does your child like to play with?
- Do tags on the back of clothes bother your child?
- Is your child interested in other children? What does your child do upon seeing another child in a park?
- When do you first remember your child pointing with 1 finger?
- Does your child play peekaboo? Will your child try to engage you?
- Does your child talk into a play telephone?
- Does your child eat a variety of foods?
- Does your child turn when you call him, her, or them?

Questions for the Physician to Ask Oneself

- What does this child's autism specific screener show?
- Do any complicating historical factors exist that may predispose this child to a developmental problem?
- Is this merely personality variation, or does this represent delays and aberrant behavior?
- Is this a language delay, or does concern exist for more social or odd behaviors?
- What should be done to evaluate?
- What types of intervention would be helpful?

Box 132.8. Common Excuses for Unusual Behaviors in Children With Suspected Autism Spectrum Disorder[a]

1. We speak 2 languages at home. (By age 3 years in a bilingual home, language should follow a normal progression. Social and unusual behaviors should always follow a normal trajectory.)
2. He is a boy. (This is accounted for in the range of normal.)
3. She is a twin. (If 1 twin has autism spectrum disorder [ASD], the other twin has an increased risk of having ASD or being delayed developmentally.)
4. He is the first child. (There is no evidence that firstborn children speak late.)
5. She is the baby. (There is no evidence that children born last speak late.)
6. He is having a bad day.
7. She watches too much television. (Neglect can result in delays, but these children still need intervention.)

[a] These are *not* reasons to delay evaluation.

disorders (eg, muscular dystrophy) can present with *language delay*, that is, isolated delay in the acquisition and expression of language.

One of the most useful examinations in the office is to simply have a conversation with an older child or play with a younger child. The physician can bring out bubbles and engage in a popping game, watching the child's eyes and observing the child's interaction with the physician and the parent or caregiver. The physician can pretend that the otoscope is a telephone that is ringing and then pick it up, talk briefly, and pass it to the child. The physician should watch the child's response. Does the child play with you, with only the bubbles, or with neither? Does the child display repetitive flapping when excited?

Laboratory Tests

No single laboratory or radiologic evaluation is diagnostic for ASD. The real keys to diagnosis are developmental surveillance, screening, and observation. Some tests are helpful to rule out comorbid conditions, however. If the child has not undergone an audiologic evaluation, that should be done first. However, the physician should not wait for audiology results before referring the patient for help. From a medical perspective, a tiered approach to the workup often is helpful. The first tier includes laboratory studies, such as a chromosomal microarray analysis (eg, comparative genomic hybridization) and a DNA test for fragile X syndrome. A lead level, carnitine profile, plasma homocysteine levels, serum amino acids, urine organic acids, thyroid evaluation, and vision evaluation should be assessed in children with global developmental delay, loss of developmental milestones, or other findings concerning for neurological or developmental disorders. If the symptoms are severe, ammonia, lactate, and pyruvate levels should also be measured. An EEG is appropriate if concern for seizures exists. The results of the newborn screening should also be reviewed. In the absence of specific clinical findings, the yield of these diagnostic studies is anticipated to be low (approximately 7%) but, if positive, may aid in the recognition of a specific comorbidity.

The second tier of tests, if necessary, includes an evaluation for specific rare diseases. Some consideration might be given to chromosomal 15 methylation, methyl CpG-binding protein 2 (in males and females), phosphatase and tensin homolog deleted on chromosome 10, fibroblast karyotype if pigmentary abnormalities are noted, sterol profile, guanidinoacetate urine analysis (only in males), or other associated genetic evaluations. According to current literature, laboratory evaluation for ASD yields an etiology in 15% of patients.

Imaging Studies

Magnetic resonance imaging should be considered for the patient with a history of regression or microcephaly, or in the presence of focal findings suggestive of central nervous system malformations; otherwise, it is considered low yield for detecting any abnormality of diagnostic significance. The child with regression, more significant involvement, or behavior suspicious of a seizure should undergo EEG. Although positron emission tomography and single-photon emission computed tomography show abnormalities, these studies are not sufficiently specific for diagnosis or to direct care. These studies are not warranted in a child with ASD; they are used primarily in the research setting.

Management

Diagnosis of ASD is sometimes challenging, but early diagnosis is critical in changing ultimate outcomes. Waitlists to see specialists and a limit on the number of specialists in this field makes it imperative for the primary care physician to be able to make the diagnosis of significant autism. The primary care physician who makes the diagnosis of ASD in a child who is older than 2 months of age with significant symptoms is correct more than 90% of the time. Because early intervention can have such a vital effect on patient outcomes, the American Academy of Pediatrics has made early diagnosis and intervention, which can reduce the cost of lifelong care by two-thirds, a priority. The diagnosis of ASD is based on the *DSM-5*.

Because children 3 years and older receive services through the local public school district, children younger than 3 years should be referred to other local governmental agencies. Most states have a government-sponsored early intervention program for children up to 3 years of age that is responsible for the evaluation of as well as the behavioral, educational, and therapeutic interventions for children with suspected delays. Such agencies offer comprehensive diagnostic evaluation and placement of eligible children in an intensive intervention program. Therefore, after a hearing test has been completed, referral to such an agency is the next step. On average, it takes 6 months from the time a child is seen in a physician's office to the attainment of such services. Thus, it is important to identify eligible children before age 30 months. Furthermore, such services are covered by private insurance in many states. It is important for primary care physicians to make such referrals.

For children older than 3 years with moderate to severe impairment, the responsibility for evaluation and treatment lies with the local school system, medical insurance, and government-sponsored agency. Even before a child is of school age, the child's local school district is responsible for the evaluation and interventions necessary to implement appropriate remediation. Physicians should verify with local agencies to determine whether such a system exists in their respective state, however. Between ages 3 and 21 years, each child is entitled to a free and appropriate education guaranteed under the federal mandate known as the Individuals with Disabilities Education Act. By law, educational programs should be comprehensive and individualized to the needs of each child. Following the assessment, teachers and other school personnel meet with parents to develop an Individualized Education Program (IEP) for the child.

Most children with ASD require, at minimum, speech and language services, occupational therapy, and social skills training. Many require a 1:1 aide in a mainstream class, and others benefit from special education services in the form of pullout or a special day class. Additional services to augment those provided in school can be given privately. Some states have mandated that medical insurance support these additional necessary services; however, in other states these additional services are the sole responsibility of the parent or caregiver.

Interventions

Autism spectrum disorder is a neurologic condition that can improve with intensive multimodality interventions. This improvement is

slow. No quick solutions, magic medications, or diets exist to "cure" ASD. Behaviors such as impulsive aggression, repetition, resistance to change, and obsession are frequently targeted by systematic interventions. Furthermore, some basic social learning behaviors can be shaped by different types of intervention. Several different techniques based on different psychological principles exist that may be used to help improve the difficulties associated with ASD (Box 132.9). The best studied therapy is known as *applied behavior analysis*, in which a child's behavior is scrutinized by a trained behaviorist and goals and trials are developed to slowly shape appropriate responses. The parent or caregiver is then taught the skills necessary for the desired outcome.

Speech and language services are vital to intervention. The initial goal is to help establish communication. In higher-functioning children who already have established language, this service is vital to the establishment and development of prosocial language, such as eye contact, inferences, understanding jokes, and the more subtle aspects of language. Social skills groups are often used to teach appropriate social responses in a seminaturalistic environment.

Occupational therapy is often necessary to help with fine motor skills and the processing of sensory information. Such therapy can be helpful in easing transitions. Although not much has been published to support the use of occupational therapy for sensory concerns, it is a widely accepted premise that sensory exposure helps children with an over- or undersensitive sensory system.

Special education in the form of an aide, classroom pullout, or special day class often is necessary to help with commonly associated learning difficulties. A child with an ASD may have a full array of learning difficulties. Commonly associated learning difficulties are in reading comprehension, written expression, and auditory comprehension; additionally, a child may have specific math disability.

Under the law, these services should occur in the least restrictive and most appropriate environment.

Box 132.9. Techniques Used in the Management of Autism Spectrum Disorder

Floortime

This intervention uses personal relationships and play in the child's area of interest to draw the child through increasingly complex developmental tasks.

Applied Behavior Analysis

Applied behavior analysis strives to achieve pre-academic skills, such as eye contact, imitation, sitting, and following simple directions using the principles of conditioning and behavioral psychology. In a 1:1 fashion, a child is trained to respond in a predetermined way using a specific curriculum and reinforcers.

Behavior Analysis

This method uses close study of behaviors to determine antecedent triggers and consequences, such as a tantrum. The goal is to substitute acceptable responses, such as using words, and increase rewards for substituted behaviors.

Pivotal Response Treatment

This strategy uses principles of behavior analysis as well as the child's interests and internal drives to motivate with the aim of generalizing the skills from a therapy room to a variety of environments. Children with an autism spectrum disorder often have difficulty performing a previously mastered skill in a new setting.

Picture Exchange Communication System

The Picture Exchange Communication System uses pictures that the nonverbal child can use to show a caregiver what the child wants.

Treatment and Education of Autistic and Related Communication Handicapped Children

The Treatment and Education of Autistic and Related Communication Handicapped Children is a complete program that incorporates the child into a large autism spectrum disorder community. The goal is to promote autonomy; the program uses many methods based on cognitive therapeutic principles.

Social Stories

These are often used as a complementary strategy. These stories describe in detail basic social skills in different scenarios.

Pharmacotherapy

The mainstay for treatment of ASD remains behavioral. Although medications do not seem to help the core symptoms of ASD, almost 2 in 3 children with ASD receive medications for behaviors that, despite intensive behavioral intervention, continue to obstruct progress or become dangerous.

Only 2 drugs have been approved by the US Food and Drug Administration for use in children with ASD. Risperidone and aripiprazole are approved for the agitation associated with this disorder. Other medications may be prescribed for other behaviors seen in children with ASD. The choice to use medication is not simple. The purpose of the medication should be to address emotional or psychological function causing the symptom. The most common medications include selective serotonin reuptake inhibitors and stimulants. However, research and clinical experience indicate that children with ASD are more sensitive to side effects and at lower doses. Therefore, the choice and direction of medication management in this population is often best guided by a developmental-behavioral pediatrician, neurologist, or child psychiatrist (see Chapter 134).

Alternative Treatments

A variety of alternative treatments have been suggested. Secretin injections, dietary restrictions, chelation, high-dose vitamins, antifungal agents, and neuron injections are just some of the interventions considered as part of alternative treatments. Anecdotal improvement has been reported with some of these methods; however, others are dangerous and have resulted in death. None of these methods is considered traditional or the standard of care, because minimal empiric data exist to support their use.

Prognosis

While many children show dramatic improvements with early intervention, others show minimal improvement. Therefore, all children need both early and ongoing intensive interventions to ensure the best possible outcome. Some prognostic indicators, such as IQ, early and intensive interventions, and a supportive family, bode

well. Obtaining an accurate IQ is often challenging. The major determinant of ultimate outcome seems to be progress in a comprehensive, early intervention program for a duration of 2 years before the child reaches age 5 years. Having little or no language by age 6 years is a poor prognostic indicator. Therefore, the goal remains focused on early identification, intensive treatment, and advocacy for children to receive such interventions with ongoing support throughout their preschool and school years.

Intensive early intervention programs have been available only since approximately 1995. Since that time, children with ASD have moved into the mainstream. Despite receiving early intervention, these children continue to have problems with transitions, more complex social interactions, and higher-level organization tasks. Thus, physicians must continue to advocate for and support these families in an ongoing longitudinal manner.

Many adults with ASD continue to require significant support. They may require sheltered living and work environments, safety monitoring, and ongoing medical support. Persons with severe ASD may receive care in group homes.

Another significant proportion of children with ASD attend college, marry, and have children. It is difficult to quantify the number of persons with ASD who achieve these milestones, because the numbers change rapidly, and the true number of children with ASD remains unknown.

CASE RESOLUTION

The child's parent completed an M-CHAT-R/F, and the child scored a 4 (ie, intermediate risk). A follow-up interview confirmed that the risk for ASD was significant, and the child was evaluated by a developmental-behavioral pediatrician and the local governmental agency, where he underwent a comprehensive assessment by a multidisciplinary team. The diagnosis of autism was confirmed, and his brother was noted to have a language delay. Both children were placed in an early intervention program. The primary patient was placed in a 1:1 structured teaching environment for 4 months. After exhibiting significant improvement, he was moved to a therapeutic preschool setting that emphasized generalization of his newly acquired skills, speech therapy, occupational therapy, and social skills. His brother received speech therapy 2 times per week. Both are due to start a regular kindergarten class in the fall, with ongoing speech and social support. The primary patient has been placed on a stimulant medication to control hyperactivity and problems with attention.

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CHAPTER 133

Attention-Deficit/ Hyperactivity Disorder

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CASE STUDY

Cody, a 10-year-old boy, has visited a primary care clinic annually for well-child care, seeing a different pediatrician each time. After falling behind his peers in all academic subjects during the first half of fourth grade, his teacher asks his mother to see if Cody's doctor can do anything to help him at school. When the appointment is made, the clinic obtains standardized attention-deficit/hyperactivity disorder (ADHD)–specific behavioral rating scales from Cody's parents and teachers. Before the visit, the pediatrician reviews these rating scales and Cody's medical history. She discovers that at Cody's 6-year well-child visit, a colleague documented, "Likely has ADHD, medication is indicated." The medical records indicate that the family deferred starting stimulant medication and were told to follow up as needed. No further mention of ADHD exists in the record. Cody also has a history of several urgent care and emergency department visits for minor unintentional injuries.

Questions

1. What are the primary symptoms of attention-deficit/hyperactivity disorder? What other conditions should be considered in the differential diagnosis of attention-deficit/hyperactivity disorder?
2. What psychiatric disorders or other neurodevelopmental disabilities commonly coexist with or mimic attention-deficit/hyperactivity disorder?
3. What is the appropriate evaluation of the child with suspected attention-deficit/hyperactivity disorder?
4. What treatment modalities are useful in the management of attention-deficit/hyperactivity disorder?
5. What is the role of primary care in the long-term management of attention-deficit/hyperactivity disorder?

Physicians should initiate a thorough evaluation for attention-deficit/hyperactivity disorder (ADHD) in any child aged 4 to 18 years who exhibits social, academic, or behavioral problems associated with inattention, impulsivity, and hyperactivity. Three types of ADHD are described in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (*DSM-5*): predominantly inattentive presentation, predominantly hyperactive/impulsive presentation, and combined hyperactive-inattentive presentation. Most children and adolescents with the disorder exhibit symptoms of the combined type. A growing body of evidence suggests that differentiating such subtypes has little bearing on prognosis or management.

The diagnosis of ADHD is based solely on clinical judgment, requiring documentation of sufficiently impairing criteria from the inattentive and/or hyperactive/impulsive domains (Box 133.1). Some symptoms of ADHD must be present before 12 years of age, and several symptoms must persist in at least 2 major contexts of the child's life (eg, home and school) for at least 6 months. These symptoms must be more frequent and severe than those typical in someone of the same developmental age and must impair the child's developmental competence, learning, or social interactions. The symptoms should not be better explained by another condition (eg, anxiety). If impairing symptoms occur at sub-diagnostic levels or are associated with a *DSM-5* exclusionary condition, a diagnosis of ADHD, not otherwise specified, should be made. Treatment, however, is symptomatic and not specific to subtype.

Transient behavioral variations, challenging temperamental features, and problem-level ADHD-like symptoms that are not frankly disordered or sufficiently impairing are better classified using the framework of *The Classification of Child and Adolescent Mental Diagnoses in Primary Care: Diagnostic and Statistical Manual for Primary Care* (DSM-PC). *Child and Adolescent Version* instead of *DSM-5* (eg, "Hyperactive/Impulsive Developmental Variation—Middle Childhood: The child plays active games for long periods. The child may occasionally do things impulsively, particularly when excited"). One advantage of the *DSM-PC* is that it takes into account specific environmental and psychosocial contexts, stressors, and developmental factors that influence children's behavior.

Epidemiology

Attention-deficit/hyperactivity disorder is the most common neurobehavioral disorder in children. An estimated 4% to 12% of school-age children have ADHD, and there exists a 3:1 predominance of boys in community samples. Over the past 2 decades, ADHD diagnoses have increased; it remains unclear whether this represents a true increase in incidence, secular changes in diagnostic criteria and practices, sociocultural bias, or effects of unspecified environmental factors.

Box 133.1. Criteria for Attention-Deficit/ Hyperactivity Disorder

Inattention[a]

- Inadequate attention to detail, makes careless mistakes
- Poor attention
- Poor or inadequate listening
- Does not follow instructions or complete assignments at school, home, or work
- Poor organizational skills
- Dislikes/avoids activities that require concentration
- Loses necessary objects (eg, homework, keys, eyeglasses, mobile telephones)
- Distractable
- Forgetful

Hyperactivity[a]

- Fidgety
- Gets out of seat (cannot sit still)
- Runs about or climbs when not appropriate
- Cannot participate in quiet activity
- Constant motion
- Excessive talking

Impulsivity

- Blurts out answer before question fully posed
- Difficulty taking turns
- Interrupts others

[a] Presence of 6 symptoms for patients age 16 years or younger or presence of 5 symptoms for patients age 17 years or older.

Derived from *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.

Clinical Presentation

Children with ADHD have problems with selective attention and mental stamina for nonrewarding or nonpreferred activities. They often make careless mistakes or fail to pay attention to details. They may be easily distracted and have difficulty starting tasks and concentrating on tasks long enough to complete them. Stopping a preferred activity also can be problematic, and caregivers often note that their children with ADHD overfocus or "get lost" in their favorite activities, such as video games, drawing, or reading. Difficulties following instructions and organizing tasks and activities are also characteristic of ADHD. Poor impulse control manifests as difficulty waiting one's turn, frequently blurting out responses at inappropriate times, and interrupting or intruding on others. Symptoms of hyperactivity include fidgetiness, excessive talking at inappropriate times, difficulty remaining seated or playing quietly, and subjective feelings of restlessness or impatience in older children and adolescents. Difficulties with social relationships and low frustration tolerance are also common among children with ADHD.

Pathophysiology

The etiology of ADHD is unknown. Interacting genetic, prenatal/perinatal, environmental/psychosocial, and neurologic factors all play a role. Family studies indicate that first-degree relatives of children with ADHD have a risk of ADHD that is 5 times greater than the risk in the general population. Additionally, measures of behavior and attention are more alike in monozygotic twins than in dizygotic twins of the same sex. The most widely confirmed gene association with ADHD is the 7-repeat allele of the D_4 dopamine receptor gene that, although found in approximately 30% of the general population, is found in 50% to 60% of individuals with ADHD. Prenatal and perinatal risk factors that have been associated with ADHD include in utero exposure to alcohol or cigarettes; extreme preterm birth; brain injury or stroke; and severe early deprivation, neglect, and maltreatment.

Currently, ADHD is conceptualized as a chronic neurodevelopmental-behavioral condition. Patients with frontal lobe lesions have long been known to exhibit severe and intractable inattention, hyperactivity, behavioral disinhibition, and impulsivity. Recent neurodevelopmental research suggests that ADHD is associated with developmental differences in specific frontal and prefrontal regions of the brain involved in executive functions, including organizing, planning, sequencing, selective attention, impulse inhibition, the ability to stick to a plan yet change it as needed (ie, set maintenance), the ability to self-talk through internal rules, and working memory. Several recent studies, some longitudinal, show delayed maturation (ie, myelination delayed) and abnormal activation/inactivation of critical prefrontal circuits and frontostriatal reward-motivation circuits in children and adolescents with ADHD compared with control subjects. Dopamine and norepinephrine are involved in neurotransmission within these brain pathways, and the prefrontal cortex is rich in catecholamine receptors. Psychostimulants can improve ADHD symptoms by increasing the availability of these neurotransmitters in the brain, thereby improving efficiency in attention and motivation circuits. Stimulants seem to primarily increase activity in key areas of the striatum, such as the ventral tegmental area, in turn activating the prefrontal cortex and executive functions.

Differential Diagnosis

The symptoms of ADHD (eg, hyperactivity, inattention, distractibility) can be seen in a variety of other conditions (Box 133.2). Sensory deficits, especially hearing impairment, can imitate attention deficits. Attention-deficit/hyperactivity disorder symptoms are often a component of autism spectrum disorder and other neurodevelopmental conditions, such as neurofibromatosis 1 or Tourette syndrome, co-occurring with typical features of the respective diagnoses, such as impaired social communication in children with autism spectrum disorder. Lead and other heavy metals have dose-related detrimental effects on behavior and development; likewise, chronic iron deficiency can result in or mimic ADHD. Seizure disorders, such as petit mal (ie, absence) or partial complex seizures, may cause altered attention or behavioral changes that can mimic ADHD. Other neurologic disorders that can present with symptoms of ADHD include Wilson disease and adrenoleukodystrophy; however, focal and often progressive neurologic deficits of acute to subacute onset are the hallmarks of these rare conditions, as opposed to the more soft and static neurologic signs of ADHD. Certain medications, such as high-dose

Box 133.2. Differential Diagnosis of Attention-Deficit/Hyperactivity Disorder

- Developmental delay or intellectual disorder
- Specific learning disorder
- Speech and language disorder
- Sleep disorder/apnea
- Sensory deficiencies (eg, hearing or vision impairment)
- Autism spectrum disorder
- Seizure disorder
- Neurogenetic syndromes (eg, neurofibromatosis 1)
- White matter disorder (eg, Wilson disease)
- Iron deficiency
- Environmental toxins (eg, lead)
- Side effects of medication (eg, phenobarbital)
- Hyperthyroidism
- Congenital infection
- In utero exposure to drugs or alcohol
- Previous brain insult (eg, stroke, trauma, infection)
- Severe family or social stresses
- Temperamental variation
- Psychiatric disorders
  - — Conduct disorder
  - — Oppositional disorder
  - — Anxiety disorders
  - — Affective disorders (eg, depression, bipolar illness)
  - — Personality disorders (eg, aggression, antisocial behavior)
  - — Substance abuse

corticosteroids, phenobarbital, and theophylline, may cause ADHD-like mental status effects, as can recreational drugs of abuse, including inhalants and marijuana. Hyperthyroidism can cause the hyperactive symptoms of ADHD, but other signs of increased metabolism, such as elevated heart rate, tremors, or weight loss, should be apparent. Exposure to alcohol or drugs in utero has been associated with subtle difficulties with learning and attention as the child develops. Congenital infections, central nervous system infections in early childhood, and traumatic brain injuries may produce behaviors similar to those that occur with ADHD. Sleep disorders, especially sleep apnea, can cause severe behavioral problems that often resolve after definitive treatment of the underlying sleep condition. Severe or chronic psychosocial-environmental stressors, such as bullying, marital discord, unemployment, poverty, homelessness, trauma/maltreatment, substance abuse, and ineffective parenting (eg, overly permissive, overly harsh), can also masquerade as, co-occur with, or exacerbate ADHD.

Children with ADHD have an increased prevalence of co-occurring pathology, which can magnify or overshadow the core symptoms of the disorder. Such pathology includes oppositional defiant disorder (35%), conduct disorder (26%), depressive disorders (18%), anxiety disorders (26%), Tourette syndrome and tics, sleep disorders (especially insomnia), fine motor delay or developmental coordination disorder, speech and language disorders, and specific learning disorders of reading, mathematics, and/or written expression. In adolescents and young adults, aggression, delinquency, and other antisocial behaviors, as well as substance abuse, often are seen together with untreated or undertreated ADHD. Children with ADHD and co-occurring conditions are well served by primary care physicians working within a multidisciplinary context, which may include developmental-behavioral or neurodevelopmental pediatricians, child and adolescent psychiatrists, child neurologists, psychologists, and therapists.

Evaluation

Children and adolescents with symptoms of inattention, hyperactivity, academic or social underachievement, or impulsivity should be evaluated first by a primary care physician, ideally one with whom the child has enjoyed continuity of care, rapport, and a strong therapeutic alliance. A complete evaluation of this nature is best accomplished with plenty of time for face-to-face review of records and a comprehensive history and physical examination; 90 to 120 minutes is a suggested minimum amount of time to do this effectively and correctly. Typically, it is necessary to schedule several appointments over the course of days or weeks.

History

The diagnostic evaluation of ADHD should begin with multiple informants (eg, caregiver[s], child, sibling[s]) giving a comprehensive medical history that includes details of the child's problem behaviors, antecedents, and outcomes and consequences (Box 133.3). The physician should learn how these informants perceive and cope with the child's behavioral problems and, in turn, how the child responds. Social/family stresses and the home and school environments should be described and evaluated and school reports and report cards reviewed. Interviewing the child alone provides an opportunity to better understand the child's own thoughts, feelings, insight, judgment, self-image, and developmental status; however, children generally have poor insight into their ADHD symptoms and generally are not considered reliable informants for *DSM-5* ADHD symptoms. Interviewing caregivers alone and talking with teachers by telephone before or after the visit can be quite helpful and alleviate some of the burden on the child of what is often initially a problem-oriented discussion about him, her, or them. The physician should inquire about the child's difficulties, developmental strengths and competencies, adaptive strategies, stress management skills, self-regulation, protective factors, and adjustment. Other important information includes developmental history (and for older children academic history, which might include school report cards or other formal assessments), family history, and sleep and diet history.

The history should cover all *DSM-5* criteria (Box 133.1). Parents/caregivers and teachers may report the child's behaviors using an ADHD-specific questionnaire or rating scale (eg, *National Institute for Children's Health Quality [NICHQ] Vanderbilt Assessment Scales*), which can be found in the American Academy of Pediatrics (AAP) publication *Caring for Children with ADHD: A Resource Toolkit for Clinicians.* Non–ADHD-specific developmental screening tools do

Box 133.3. What to Ask

Screening for Attention-Deficit/Hyperactivity Disorder

- History of presenting complaint (from multiple informants)
  - What concerns do you have about the child's development, behavior, or learning?
  - How is the child doing in school academically and socially?
  - Is the child happy in school?
  - Has the child been held back in any grade, suspended, dropped out, or considered dropping out?
  - How often does the child have problems completing home chores, class work, or homework?
  - How often does the child have major problems controlling his or her behavior at home, in school, or with friends?
  - How often is behavior management, self-regulation, or discipline difficult at home or school?
  - What are the antecedents and consequences for problem behaviors at home and school? What discipline techniques have been tried, and what effects did each have?
- Perinatal, developmental, academic, and medical history
- Psychological history and previous treatments
- Social and environmental history
- Family history, with particular focus on immediate family attention-deficit/hyperactivity disorder, school problems, developmental delays, conduct problems, and cardiac, musculoskeletal, neurologic, or psychiatric conditions

not replace this type of comprehensive ADHD assessment because their sensitivity and specificity for ADHD are inadequate. For younger children (aged 4–7 years), few validated screening tools exist (eg, *Conners Comprehensive Behavior Rating Scales*, *ADHD Rating Scale-IV*). Questionnaires can suggest a diagnosis but are insufficient to confirm a diagnosis; only clinical interview and observation can definitively confirm or rule out ADHD.

The physician should evaluate for coexisting conditions that would warrant further investigation. Broad screening tools, such as the Child Behavior Checklist; Behavior Assessment System for Children, 2nd Edition; Strengths & Difficulties Questionnaires; or Pediatric Symptom Checklist, can be useful in this endeavor. For example, frequent sadness or isolation is suggestive of depression, and persistent negative, hostile, and defiant behavior toward authority is suggestive of oppositional defiant disorder. The AAP toolkit for clinicians includes a scale specific to ADHD behaviors and a broader scale for possible coexisting conditions.

Physical Examination

The child's weight, height, and head circumference should be plotted on a growth curve and the pattern of growth evaluated; pubertal status should be recorded. The child should be examined for congenital anomalies, syndromic stigmata, or dysmorphic features, such as fetal alcohol facies or café au lait skin macules. A cardiac examination should document pulses and heart sounds. A musculoskeletal evaluation should document bulk, strength, tone, gait, station, and fine and gross motor coordination; a neurologic examination should include assessment of the cranial nerves; sensation, including hearing and vision; balance and proprioception; and repetitive movements, tics, or tremors. The psychiatric and behavioral status examination should include an assessment of parent/caregiver-child interactions and the child's temperament, mental status, affect, mood, insight, judgment, social-emotional reciprocity, joint attention, speech/language and communication, memory, fund of knowledge, and thought content and processes.

Observing the child's behavior during the office visit is crucial, with the caveat that many children with ADHD do not appear grossly hyperactive or inattentive in the office. Nevertheless, interaction between the child and the parents or caregivers should be observed and documented. The physician should note how the child deals with complex parental and examiner instructions, directives, and questions and how parents or caregivers respond to any misbehavior. Does the child cooperate and comply with the examination, and does the child seem motivated to change? How well does the child relate to adults? The physician should observe the child playing (eg, drawing, playing with toys) and note the child's organization of activities, attention span, distractibility, impulse control, and motor activity.

Laboratory Tests

Diagnostic tests, such as specific neuropsychological or psychiatric metrics (eg, IQ tests), are not indicated for initial ADHD evaluations and should be guided by selected findings on the history and physical examination. Psychometric testing or standardized school district tests may show that a discrepancy exists between the child's raw abilities (eg, IQ) and academic progress in 1 or more areas (eg, achievement scores, grades); in such a case, a referral for psychoeducational testing to rule out specific learning disabilities is indicated. If indicated, the child should be referred for further evaluation of speech, hearing, and vision. Similarly, blood tests, such as hematocrit, lead level, and thyroid hormone are indicated only in the setting of relevant signs or symptoms. Additionally, computerized continuous performance tasks designed to measure vigilance or distractibility have low sensitivity and specificity and do not adequately differentiate children with ADHD from control subjects.

Currently, brain imaging (eg, magnetic resonance imaging, positron emission tomography) has no role in the evaluation of ADHD. Despite the utility of such measures in population-level studies, they cannot yet accurately differentiate between the brains of individuals with and without ADHD. Electroencephalography or neurologic consultation is indicated only if absence or partial complex seizures are suspected based on the history or physical examination.

Management

Attention-deficit/hyperactivity disorder is a chronic condition; thus, management of it must be multimodal, continuous, and longitudinal. Because of its chronicity, ADHD is a special health care need that should be managed within a medical home model. Frequent

follow-up—at least quarterly—and consistent management is the key to sustaining the benefits of behavioral and pharmacologic treatments for ADHD. Family education should emphasize the strengths of children and families and address parental/caregiver concerns; additionally, physicians should foster a close working relationship between families and their children's school systems. Families should be aware that children with untreated or undertreated ADHD often experience functional impairments in academic achievement, self-esteem, social skills, peer status, and family relationships; more unintentional injuries; and above-average use of emergency departments. The physician can ease parents' or caregivers' guilt by explaining the neurodevelopmental basis of ADHD and assuring that ADHD is not the result of insufficient parenting. Children who discover that their problems are explained by a medical condition may feel that a heavy burden has been lifted from their shoulders. However, parents/caregivers and children may find it difficult to accept that the child has a chronic disorder. Support groups and parent/caregiver training through organizations such as Children and Adults with Attention-Deficit/Hyperactivity Disorder (www.chadd.org) may be helpful for families. Physicians should work together with the child, family, and school personnel to specify appropriate target outcomes. Parents and school personnel should then monitor the child for target behaviors and adverse effects. If target outcomes are not met, the physician should reevaluate the initial diagnosis, the use of available treatments, adherence to the plan, and the potential for coexisting conditions.

Behavior Management

Behavior management should be the first-line treatment for preschool-age children with ADHD. Behavioral treatment may also be effective for older children, particularly those with anxiety or disruptive or oppositional problems. Recent studies suggest that initial treatment with behavioral modification therapy (also known as behavioral parent training) is generally more beneficial and more cost-effective than beginning with medication therapy for children ages 5 through 12 years. The goals of behavior management are to modify the child's physical and social environment at home and school to influence positive behavioral change. Behavioral modification techniques include rewards for the target outcome behaviors (eg, verbal praise; hugs; points or stars on a chart that can be traded for material objects or a desired activity, such as a game or special time with a parent or caregiver) and punishments for unacceptable behaviors (eg, time-out, loss of a privilege, extra chores, reduction in allowance). Acceptable and unacceptable behaviors should be clearly defined and measurable, and rewards and punishments should be spelled out in a contract drawn up with input from the child. The strongest behavioral interventions follow immediately after a behavior (eg, immediate praise when a child follows a command after the first time it was given). If rewards or punishments are used over time, parents/caregivers and teachers must be creative in periodically varying the rewards and penalties. Management of overactive children who have difficulty focusing attention, following rules, and controlling impulses can be challenging for parents/caregivers and teachers. The best results come from praising and reinforcing positive behaviors and ignoring negative behaviors unless the latter are dangerous or intolerable. Using praising and ignoring in combination can be quite successful. Parent or caregiver commands should be clear and countable, such as, "You need to go upstairs to brush your teeth before the egg timer goes off in 3 minutes." Because children with ADHD can have difficulty carrying out multistep commands, it is best to set them up for success by giving clear, doable, single-step commands. Behavior management in combination with medication management can be extremely effective. Potential benefits of behavioral therapy when used concurrently with medication include improved scores on some academic measures, improved behavior, and decreased anxiety symptoms. Approaches that target executive function training and cognitive-emotional self-regulation may also be useful adjuncts. Interventions such as play therapy, psychotherapy, and cognitive therapy have no documented efficacy in managing core ADHD symptoms; however, they may be indicated for common co-occurring conditions, such as anxiety, conduct disorder, and depression.

Educational Interventions

The pediatrician can improve the child's educational experience by contacting the child's teachers and even attending school conferences and special education meetings. Although most children with ADHD can be accommodated in the regular classroom, special education in a smaller, more focused setting may be indicated for the child with behavioral or academic difficulties.

Teachers can use specific strategies to help children with ADHD focus their attention and follow directions in the classroom (Box 133.4). Behavioral therapy should be integrated into the classroom, focusing on a child's strengths and minimizing stigma. Teachers and caregivers who are most successful in working with children with ADHD are able to set firm limits and discipline children without anger or frustration, while at the same time remaining flexible enough to recognize when a change in tactics or even "rolling with it" is necessary. Caregivers of children with ADHD can request needed classroom accommodations through Section 504 of the Americans with Disabilities Act of 1990, and children whose ADHD symptoms cause significant learning deficits may qualify for an Individual Education Program through the Individuals with Disabilities Education Act. A letter from a primary care physician documenting a child's health impairments, developmental risks, and academic limitations attributable to ADHD can have a considerable effect in helping to ease this process for families and schools. Preschool-age children with ADHD should be referred to early intervention services in their school district to see if they qualify for educational services that would help prepare them for kindergarten entry.

Because children with ADHD are easily provoked into misbehavior and are prone to clashes with peers, they can also benefit from closer supervision in unstructured school areas, such as the playground, cafeteria, halls, and school bus. Programs designed to improve social competence and peer relationships (eg, group social skills training, therapeutic recreational activities) may also be helpful.

Box 133.4. Strategies for Managing the Behaviors of Children with Attention-Deficit/Hyperactivity Disorder in the Classroom

- Seat children where distractions are minimized and where teachers can see how and when children are paying attention.
- Cue children discretely or nonverbally to remind them to refocus their attention.
- Give clear, succinct, 1- to 2-step directions, and repeat them frequently and patiently.
- Break up work periods by allowing children to get up and move around (eg, handing out papers, cleaning blackboard or whiteboard).

Box 133.5. Stimulant Medications for Use in Managing Attention-Deficit/Hyperactivity Disorder[a]

Methylphenidate Hydrochloride

- Short-acting
  - — Pill: Ritalin, Methylin, Focalin
  - — Chewable: methylphenidate hydrochloride chewable
  - — Liquid: Methylin solution
- Intermediate-acting
  - — Pill: Ritalin SR, Metadate ER, Methylin ER
  - — Chewable: QuilliChew ER
- Long-acting/extended release
  - — Pill: Apetensio XR, Concerta, Metadate CD, Ritalin LA, Focalin XR
  - — Chewable or dissolvable: Cotempla XR-ODT
  - — Liquid: Quillivant XR
  - — Transdermal: Daytrana

Amphetamine

- Short-acting
  - — Pill: Dexedrine, Dextrostat, Desoxyn, Evekeo, Zenzedi
  - — Liquid: ProCentra
- Intermediate-acting
  - — Pill: Adderall, Dexedrine Spansule
- Long-acting/extended release
  - — Pill: Adderall XR, Vyvanse
  - — Liquid: Dyanavel XR
  - — Dissolvable: Adzenys XR-ODT

[a] Short-acting (3–6 hours), intermediate-acting (6–8 hours), and long-acting (10–12+ hours).

Pharmacotherapy

Research has shown that psychostimulant medication with and without behavioral therapy is efficacious in reducing the core symptoms of ADHD. Furthermore, some evidence exists that these effects translate into an increased ability to follow rules as well as improved classroom behavior and improved relationships with peers and parents or caregivers; the effects on higher-order executive functions are less predictable, however. The effects of stimulant medication on learning are not well studied. Caution should be used when treating children younger than 5 years or weighing less than 20 kg (<44.1 lb) with stimulant medication, because many pharmaceutical stimulant preparations have narrower therapeutic windows and more adverse effects on a per-kilogram basis for children of smaller stature. However, for preschool-age children without access to behavioral treatment or with frequent dangerous impulsive behaviors, methylphenidate hydrochloride has been well-studied in randomized controlled trials and can be considered first-line treatment if the physician believes that the benefits outweigh the risks.

Psychostimulant medications are the most commonly used agents for ADHD and have by far the most evidence-based research to support their use. Currently available stimulants include short-acting (3–6 hours), intermediate-acting (6–8 hours), and long-acting (10–12+ hours) formulations of methylphenidate hydrochloride and amphetamines (Box 133.5). Studies have found few, if any, differences between the efficacy of methylphenidate hydrochloride and amphetamine, but some children will respond better to, or have fewer side effects with, 1 or the other.

Stimulants affect behaviors within 30 to 60 minutes and affect attention (eg, for a school subject such as math) within 1.5 hours after administration. There is little evidence of tolerance to stimulants over time, but short-term tolerance occurs so that blood levels must remain therapeutic during the day to maintain efficacy. Therefore, it is best to use long-acting stimulants that eliminate the need to take medication at school. In addition, the effect of long-acting stimulants may persist during after-school homework time. A transdermal delivery system and liquid formulations are available for some stimulants.

The most common side effects of stimulant medications are decreased appetite, stomachache, headache, delayed sleep onset, and jitteriness; side effects occur in 4% to 10% of children. Less common side effects include severe emotional lability/sadness or agitation, transient rebound irritability or hyperactivity (as the medication wears off), delusions or mania, and hallucinations (especially somatic creepy-crawly feelings). Transient motor tics may occur while on the medication, or an existing chronic tic or Tourette syndrome may be exacerbated or unmasked. At higher doses, stimulants can negatively influence height velocity and may slightly decrease predicted adult height. Although dosing of stimulant medication is based on individual variation in response, researchers have found that children generally do better on a maximized tolerable dose of stimulant medications, which is body-weight dependent, rather than the lowest dose that shows a clinical effect. Thus, the best stimulant dose for an individual child is the dose that produces near-complete symptom remission while producing acceptable side effects (eg, appetite suppression is usually tolerable, whereas growth suppression is not). For this reason, it is recommended that physicians do a controlled open-label titration trial of multiple dosages of a single agent using a systematic method. For example, a physician might use either long-acting methylphenidate hydrochloride in 18-, 36-, and 54-mg dosages or long-acting amphetamine in 10-, 20-, and 30-mg dosages in 1-week blocks, with teacher- and parent-/caregiver-completed *DSM-PC* based rating scales (eg, *NICHQ Vanderbilt Assessment Scales*) at the end of each week. The physician can then use these scales to develop a medication management plan with the family. Published guidelines and algorithms, such as those from the AAP, can aid the physician in this regard.

After the medication dosage is stable and helpful, often after 2 to 4 visits over 1 to 2 months, follow-up should occur at least every 3 to 4 months, with particular attention to emerging developmental competencies, self-mastery, and improvement in targeted goal behaviors. Such visits should minimally include an interim history, weight, height, blood pressure, and scales of clinical response from caregivers and teachers.

If a particular stimulant does not produce symptom remission at all or does so only with severe or intolerable adverse effects, the physician should systematically try 1 or 2 other stimulants, because 70% to 80% of children achieve complete remission of symptoms in this manner. If 2 or 3 psychostimulants are not effective or produce unacceptable or intolerable side effects, other medications can be used. Atomoxetine hydrochloride (Strattera) is a nonstimulant medication that selectively inhibits the norepinephrine transporter. It is approved for children older than 6 years, has once-daily dosing, should be titrated to an effective weight-based dose, and often takes 1 to 6 weeks to produce effects; adverse effects can include gastrointestinal upset and mood irritability. Alpha$_2$-agonists, such as clonidine hydrochloride (Catapres, Kapvay) and guanfacine hydrochloride (Tenex, Intuniv), are often useful as adjuncts for children with poorly controlled hyperactivity/impulsivity or comorbid tics, although few children with ADHD achieve adequate symptom remission on α_2-agonist monotherapy. Tricyclic antidepressants, selective norepinephrine reuptake inhibitors, or bupropion hydrochloride can have positive effects on ADHD symptoms for some children, although these medications are rarely used as monotherapy and are typically fourth-line agents. Pemoline (eg, Cylert) is generally not used because of the potential for fatal hepatotoxicity and is no longer manufactured as of 2005. Similarly, generic pemoline is no longer being manufactured. Modafinil, mood stabilizers, antiepileptic agents, and atypical antipsychotic agents are generally not indicated in the management of ADHD in the primary care setting.

Complementary and alternative medicines, such as vitamins, dietary restrictions, and occupational therapy or sensory integration, are used by 54% of parents/caregivers, but only 11% discuss these with their child's clinician. Primary care physicians are challenged to help families safely navigate the limited evidence available on the risks and benefits of such therapies. For example, melatonin is safe and often helpful for comorbid sleep disorders prevalent in children with ADHD, and eliminating artificial colors from the diet may help children who are sensitive to the effects of those artificial colors on their activity level. Some popular holistic approaches, such as behavioral optometry and the Feingold elimination diet, have either no evidence to support them or have evidence indicating that they should not be used. Finally, although neurobehavioral toxicity may be associated with low doses of various environmental toxins, particularly in young children, pediatricians are encouraged to emphasize primary prevention; chelation has no role in this context.

Prognosis

Attention-deficit/hyperactivity disorder is a chronic condition, persisting into adolescence and adulthood in approximately two-thirds of affected children. Children and adolescents with ADHD can succeed in school, at home, and with their peers when provided longitudinal, comprehensive care within a medical home. Biweekly to monthly visits are recommended during the initial phase of assessment and management as well as whenever medications or therapies are changed. Thereafter, quarterly visits (or more frequently as indicated) are ideal because more frequent follow-up is associated with improved long-term outcomes. Gathering information in an ongoing fashion from multiple informants is a critical part of such follow-up (eg, periodic ADHD symptoms checklists from teachers). Primary care for children and youth with ADHD and their families can be enhanced through clinical systems improvements, such as integrated behavioral health, care coordination, and rapid access for patients with behavioral crises.

Overall, adults whose childhood ADHD went untreated or undertreated complete less schooling, hold lower-ranking occupations, have lower self-esteem and more social-skill deficits, and exhibit more antisocial behavior and alcohol and drug abuse. High-quality health care can improve and possibly reduce sociodemographic disparities in these outcomes for youth with ADHD. Having ADHD does not preclude attaining high educational and vocational goals, and some adults who had childhood ADHD no longer meet full *DSM-5* criteria. Typically, hyperactivity greatly diminishes or resolves in high school or early adulthood; some young adults experience a bothersome sense of inner restlessness. Attention problems and impulsivity may continue or worsen, to varying degrees. Adults with ADHD may choose occupations that match their strengths and minimize limitations (eg, on-the-road salesperson vs desk-job accountant). Although up to 50% of adults with ADHD choose to continue medication, others function well without medication; many continue to engage in psychological therapies to help manage daily life tasks, such as money management, and/or for co-occurring conditions, such as anxiety.

CASE RESOLUTION

Cody's primary care clinic reorganized its system of care to leverage the core concepts of the medical home to improve care for children with chronic conditions, including ADHD. One of the clinic's nurses, Karen, has been trained to coordinate referrals to behavioral health and other specialists as indicated, communicate and coordinate care with schools and community services, and monitor adherence and response to treatments.

During Cody's visit, the pediatrician confirms the diagnosis of ADHD and probable comorbid anxiety using AAP clinical practice guidelines and standardized criteria. She educates Cody and his family about multimodal evidence-based interventions for these conditions and introduces the family to Karen and the medical home model of care. Karen follows up with the family by telephone 1 week later as planned and learns that they are reluctant to start Cody on any medicine. She guides Cody's parents to voice their preferences and cultural perspectives on possible interventions and assists them in making another appointment with the same pediatrician, thereby ensuring continuity of care. At the next visit, the pediatrician uses motivational interviewing to help the family find agreement on a watchful waiting approach with close, continuous school and home follow-up by Karen and at least quarterly visits with the same pediatrician. One month later, after a behavioral crisis at school, Cody's parents request an urgent appointment with same-day access. The pediatrician reviews recent parent and teacher behavioral rating scales at the point of care (gathered by Karen the week prior) and reiterates the available first-line treatment options. The family agrees to pursue an open titration trial of stimulant medication for ADHD symptoms and referral to a therapist who is familiar with behavioral parent training, for evaluation and possible treatment of the anxiety symptoms. Another clinic visit is scheduled in 1 month, and meanwhile, Karen continues to follow up weekly with Cody's parents, teachers, and therapists.

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CHAPTER 134

Psychopharmacology in Children

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CASE STUDY

An 8-year-old girl has been diagnosed with high-functioning autism spectrum disorder. The local developmental-behavioral pediatrician has recommended treating her anxiety and inattention with atomoxetine hydrochloride. The girl's mother is quite hesitant to do so. She trusts you, however, and wants your opinion.

Questions

1. What is the means by which the safety and appropriateness of psychotropic medications is assessed?
2. What type blood tests are used to maximize safe administration and how often are they performed?
3. What factors should be considered when placing a child on psychotropic medications?
4. What are the usual side effects of commonly used psychotropic medications?

Psychopharmacologic agents are being used with increased frequency in the pediatric population. Approximately 50% of children and adolescents will, at some point before age 18 years, meet criteria for a psychiatric diagnosis. Almost 25% of children will have substantial impairment as a result of those symptoms. Unlike antibiotics or other medications used in children, psychopharmacologic agents are used daily and for extended periods. Furthermore, it is important to recognize the dearth of evidence-based information supporting the use of many medications in children, including psychotropic medications. Therefore, many of these medications are used in an off-label fashion. The medical community must rely on published data (often in adult subjects), clinical experience, and expert consensus to guide medication choice, dose, and management. This often provokes parental anxiety and sparks numerous concerns from families who do not understand that the US Food and Drug Administration (FDA) label limits the claims a manufacturer can make but does not limit a physician's use of medications. Furthermore, families are often anxious, because physicians rely almost exclusively on history and structured behavioral observation, which is the most important "test" for most of these disorders. Unfortunately, the United States has a shortage of pediatric subspecialists trained to choose, monitor, and manage these medications for children. Pediatricians often serve as the first point of contact with families. In most cases, many months may elapse before families are able to see a child and adolescent psychiatrist for diagnostic evaluation and medication management. It is, therefore, necessary for pediatricians to be familiar with the common psychiatric conditions, different classes of psychotropic medications, and controversies facing families of affected children.

Pediatricians need to understand the principles guiding the use of these medications and become familiar with some of the more frequently used psychopharmacologic agents. The most used classes of medication in children include stimulants, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs) and atypical antipsychotics, also known as serotonin-dopamine antagonists (SDAs). This information can also be useful in helping families navigate this confusing maze.

The decision to use psychopharmacologic agents should be made only after obtaining a comprehensive history as well as a physical and mental status examination and making an accurate diagnosis. It is imperative to obtain collateral information from parents or caregivers, school, and/or therapists. Rating scales can be used as screening tools, as tools for establishing a baseline, and for monitoring progress and treatment response. For common psychiatric conditions, such as depression and anxiety, referral to therapy is indicated. If the symptoms and associated impairments are moderate or severe, however, medication management is necessary, often in addition to therapy. Medications should be an integral part of a comprehensive treatment program that addresses the academic, behavioral, medical, and developmental needs of the child. The decision to place a child on any agent should be based on significant dysfunction as well as discussion and full disclosure of potential risks and benefits with the parents or caregivers and the child. A medication trial, once undertaken, should be carefully monitored, methodically addressing adverse events and effectiveness. Generally, it is best to change 1 agent or dose at a time, followed by structured observation (eg, rating scale[s]) to determine the effect of the change. Therefore, a physician usually begins with monotherapy, optimizes the dose over

the recommended period of time, and assesses risks and benefits before developing a more complex regimen. Such a trial necessitates frequent visits and discussion with the administering physician. Current scientific information and clinical experience indicate that the use of psychopharmacologic agents in young children (<5 years) should be reserved for extraordinary circumstances.

Children are not little adults. Pharmacokinetics in children is affected by increased rates of metabolism in their relatively larger livers, a faster glomerular filtration rate, and variable fatty tissues. Some children, therefore, require a dose larger than that used in adults. Conversely, perhaps because of size, fat distribution, and other explanations, a much smaller, and seemingly ineffective, dose may be sufficient. In general, it is recommended to start low and go slow to prevent adverse effects of medication. For most agents, little correlation exists between blood level and treatment response. Furthermore, some medications have a duration of effect that well exceeds the half-life (eg, atomoxetine hydrochloride); however, with other medications (eg, stimulants) the effect diminishes despite a significant level of the agent in the blood. Additionally, for most agents (eg, stimulants, SDAs), no correlation with milligrams per kilogram exists. Frequent clinical monitoring and communication with parents/caregivers and family and often with teachers and therapists as well are vital to understanding response to medication, tolerance, and treatment adherence.

Psychostimulants

Psychostimulants are the most studied psychotropic medications used in pediatrics (see Chapter 133). These medications are used to manage the hyperactivity, inattention, and impulsivity that occur with attention-deficit/hyperactivity disorder (ADHD) and disturbances of attention that occur in other disorders (eg, autism spectrum disorder [ASD], traumatic brain injury, depression). Stimulants are also used in the management of narcolepsy. During the past decade, many new delivery systems have been developed with differing durations of action, which help to cater to the specific lifestyle needs of the patient. Much work has been done to determine optimal blood level delivery resulting in the most consistent effect. Overall, the duration of action and clinical efficacy are more relevant than the blood level in this class of medication.

The mechanism of action of psychostimulants is to increase dopamine and norepinephrine in the synapse. Overall, this enhances activity in the prefrontal cortex of the brain responsible for attention, focus, and executive function (ie, organization and planning).

Substantial evidence exists in multisite, double-blind, placebo-controlled studies (eg, Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder) to support the first-line use of these medications in the treatment of school-age children and adolescents with ADHD. Evolving evidence exists (Preschool Attention-Deficit/Hyperactivity Disorder Treatment Study) to support the use of these drugs in preschool-age children. Medications may be helpful for preschool-age children for whom an adequate trial of behavior therapy has been unsuccessful. A growing body of evidence supports their use in ASD, albeit at lower doses because of the lower threshold for side effects.

Parents and caregivers have varied concerns related to stimulants, many of which are propagated by the media; however, leaving ADHD untreated results in significant comorbidities and risks for negative outcomes. Attention-deficit/hyperactivity disorder in children and adolescents has been associated with academic underachievement, grade retention, and ultimately, school dropout in several studies as well as an increased risk for substance use disorders. Nonetheless, several areas of controversy exist and often become a primary focus for hesitant parents or caregivers. Understanding the facts can help demystify these medications for parents or caregivers. For example, a risk of substance abuse has long been linked with stimulant medication. A substantial body of evidence shows that the use of stimulant medication does not result in an increased risk of later substance abuse. In fact, it is untreated ADHD and the resultant development of maladaptive behaviors that places adolescents at increased risk for substance use disorders. The hypothesis is that management of ADHD with stimulant medication in fact reduces substance use and many other potential negative outcomes, such as early tobacco use, undesired pregnancy, and motor vehicle crashes. Because stimulants often are prescribed for extended periods of time, however, additional long-term studies are needed.

Another frequently raised concern is the association between stimulants and an increase in sudden unexpected deaths. This would raise concern for any parent or caregiver. However, FDA scrutiny of these statistics revealed a lower incidence of sudden unexpected deaths in individuals on stimulants compared with the unmedicated population. Persons who died tended to have an underlying cardiac defect. Based on the current evidence, the American Academy of Pediatrics and the American Heart Association recommend a detailed cardiovascular history, a family history, and a physical examination followed by the initiation or continuation of pharmacotherapy with ADHD medications without further assessment in patients whose history and examination are not suggestive of cardiac disease. In individuals with a positive personal or family history and/or physical examination for cardiac disease, further evaluation is necessary, consisting of electrocardiography (ECG) and/or consultation with a pediatric cardiologist. After treatment is initiated, children and adolescents must be monitored for changes in heart rate, blood pressure, and cardiovascular symptoms during treatment.

Historically, height suppression has been raised as a concern with these medications. Numerous studies have tried to answer this question. A recent longitudinal study of more than 10 years' duration supports an initial growth suppression emphasized in the first 3 years of treatment that appears to resolve over the remaining 7 years. Parents or caregivers can be further reassured that if height suppression does occur, it seems to be minimal (eg, a median loss of <0.2 standard deviations over 2–3 years) and tends to attenuate with increasing time on treatment for both methylphenidate hydrochloride and amphetamine formulations. It is preferable for patients to graduate from high school even if their final adult height is slightly lower than that predicted by parental stature. Another 10- to 11-year longitudinal study that assessed the effect of ADHD and its treatment on growth outcomes in children followed into adulthood did

not support an association between deficits in growth outcomes and ADHD or psychostimulant treatment for ADHD. However, it is important to monitor growth in routine follow-up visits.

Finally, many parents and caregivers are concerned that their children will be "zombies" on medication. Children who are overmedicated can appear glassy-eyed and overly passive; however, good communication and interaction between families and doctors will quickly alleviate this problem. Families who often want to try alternative therapies are routinely encountered in clinical practice. Families should be educated about the potential risks of alternative therapies and continually encouraged to use evidence-based pharmacotherapeutic and/or psychotherapeutic measures simultaneously. Additionally, families may have concern about worsening tics with use of stimulant medications. A recent meta-analysis concluded that most patients with ADHD and a tic disorder benefit from moderate doses of stimulant treatment without worsening of tics and that the addition of α_2 agonists was especially useful because they were therapeutic for both ADHD and the tic disorder. Additional information about these medications may be found in Chapter 133.

Selective Norepinephrine Reuptake Inhibitors

Currently, the SNRIs include 1 medication that is frequently used in children: atomoxetine hydrochloride (eg, Strattera). Atomoxetine hydrochloride is used in the management of ADHD and for the inattention and anxiety associated with ASD.

The mechanism of action for atomoxetine hydrochloride is to block the reuptake of norepinephrine in the synapse. This may have a direct effect on enhancing the signal-to-noise ratio in the brain and may also ultimately result in an increase in dopamine in the prefrontal cortex of the brain. Unlike stimulant medications, atomoxetine hydrochloride avoids the nucleus accumbens so that it has no abuse liability.

Atomoxetine hydrochloride was originally studied as an antidepressant agent, but early investigation did not yield robust antidepressant effects. Marketed as providing "continuous symptom relief," a careful duration of action study shows little effect on core ADHD symptoms after 9 hours; however, some possible other small effects (eg, compliance) may last slightly longer. The attractiveness of atomexitine hydrochloride stems from its identity as an FDA-approved non-stimulant. Although usually less effective than stimulants, it has a different side-effect profile and may be associated with slight mood and anxiety benefits.

Research shows that atomoxetine hydrochloride, which is FDA approved for use in patients with ADHD, is effective in managing symptoms of this disorder for a given individual but has been found in studies of groups of people to be less effective than stimulant medications. Atomoxetine hydrochloride generally has a 60% response rate (measured by 25% reduction in ADHD ratings), compared with a 70% to 80% response rate (measured by 30% reduction in ADHD ratings) with stimulant medications. Furthermore, 3 different studies in which atomoxetine hydrochloride was directly compared with stimulants have demonstrated atomoxetine hydrochloride to be less effective on average, even though, as stated previously, some individual patients do well with this medication. Atomoxetine hydrochloride should especially be considered for patients in whom use of a stimulant was unsuccessful (eg, poor tolerance or poor effect of a trial on a methylphenidate hydrochloride preparation and a trial on an amphetamine preparation), significant history of substance use and diversion, exacerbation of tic disorder with stimulants, and the presence of comorbid anxiety disorder.

The side effects of atomoxetine hydrochloride are quite similar to those of traditional stimulants, with the added concerns of drowsiness, dizziness, and cough. Furthermore, similar to SSRIs, atomoxetine hydrochloride carries a warning citing a slightly increased risk of suicidal ideation. It is important for physicians to monitor for changes in mood, irritability, agitation and suicidality, especially during first 4 to 5 months of therapy. Atomoxetine hydrochloride is not associated with tic exacerbation. Response to this medicine is more like that of an antidepressant in that it may take 4 to 6 weeks to see the full effect of a particular dose. Drug holidays are not an option with this medication. The dosage range is 0.5 mg/kg to 1.8 mg/kg. Individuals on the autism spectrum tend to respond at lower doses and with a lower threshold for adverse side effects.

A few patients have reportedly experienced a serious idiosyncratic reaction suggestive of liver failure. These patients were on FDA-approved doses of atomoxetine hydrochloride for several months. They experienced vomiting, jaundice, and elevated liver enzymes. These findings resolved when the medication was discontinued and returned with reexposure to the drug. This finding resulted in an FDA warning to consider potential liver failure in a vomiting patient on atomoxetine hydrochloride. If the patient develops jaundice or laboratory signs of hepatic injury, the medication should be discontinued.

The American Academy of Pediatrics and American Academy of Child and Adolescent Psychiatry recommend stimulants as first-line treatment for ADHD. Neither blood nor urine test monitoring is necessary for either stimulants or SNRIs. The physician should regularly monitor improvement, adverse events, and adherence using rating scales; this should be done at least every 3 months after both dose and agent have been optimized.

Parents and caregivers often want to know if these medications can be used intermittently and stopped as soon as possible. With stimulants and SNRIs, results are optimized when these medications are administered 7 days a week and without large breaks. Longitudinal studies suggest that although some symptoms may resolve over time, significant impairment from even a small number of symptoms persists into adulthood for 60% to 70% of those diagnosed with ADHD. Inattention is more likely to persist into adulthood. Therefore, many people may continue on medication for several years. To assess for continued benefit, a break from medication may be attempted annually. As children grow larger, they often need higher doses. However, as compensatory mechanisms develop and some symptoms subside, some patients may require less medication. It is beneficial to re-optimize doses and agents throughout

the length of treatment. Drug holidays have no established intrinsic value on their own and should be recommended only for children with significant medication side effects, such as substantial weight loss. If a parent or caregiver is requesting a drug holiday, it is a signal that the parent or caregiver may need to review the value of the medication. A discussion should ensue as to whether the parent/caregiver and child continue to see benefit, the patient is having troubling side effects, or the medication at any dose is not helpful and is associated with concerning symptoms. The physician must take into consideration the knowledge that atomoxetine hydrochloride, once stopped and restarted, needs time to reachieve a therapeutic level.

Box 134.1. Disorders Managed With Selective Serotonin Reuptake Inhibitors

- Depression
- Obsessive-compulsive disorder
- Generalized anxiety disorder
- Separation anxiety disorder
- Panic disorder
- Selective mutism
- Posttraumatic stress disorder
- Autism spectrum disorder
- Bulimia

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors are frequently used in children and adolescents to manage a variety of depression- and anxiety-based symptoms (Table 134.1) (Box 134.1). Similar to SNRIs, SSRIs block presynaptic reuptake of serotonin after it is released into the synapse, thereby enhancing serotonin activity in the synapse. Empirical evidence has established the benefit of SSRIs in the management of depressive and anxiety disorders.

Medication is not a substitute for therapeutic support. In fact, most clinical guidelines recommend psychotherapy as first-line treatment for mild and moderate anxiety and depressive disorders in children. Medication management should be undertaken only if psychotherapy progress is minimal or symptom severity and impairment are moderate to severe. Most studies have proved that combination treatment of medication and therapy is more effective than either treatment modality alone. Obsessive-compulsive disorder is a unique anxiety disorder that typically requires higher doses of SSRIs than do anxiety or depressive disorders. The chronicity of the condition with the possibility of frequent exacerbations necessitates the use of a specific type of cognitive behavioral therapy, namely, exposure and response prevention.

Medications are chosen based on side-effect profile and half-life. Because of a significant placebo effect and a lack of multiple, large, highly powered studies in children, only a few medications have received FDA approval for use in children (Table 134.1). Numerous studies exist that may not meet strict scientific criteria but, taken together with vast clinical experience and consensus, imply reasonably well-tolerated and beneficial effects of these medications. Studies have consistently found SSRIs to be more effective and safer than tricyclic antidepressants as a treatment for depression.

Selective serotonin reuptake inhibitors are metabolized via the liver through the cytochrome P-450 system. Individual enzyme variations exist that result in variable metabolism of any of the many medications that travel through these pathways. Overwhelming this system may cause inhibition and buildup of medications or facilitated rapid metabolism of others. Thus, monitoring of all medications

Table 134.1. Selective Serotonin Reuptake Inhibitors

Generic	*Trade Name*	*FDA Pediatric Approval*	*Suggested Pediatric Dose, mg*	*Half-life*	*Increase Increment (After 4 Weeks)*	*Time Steady State, days*
Fluoxetine	Prozac	Depression/OCD	5–60[a]	4–6 days	5–20 mg[b]	28–35
Sertraline hydrochloride	Zoloft	OCD	25–200[a]	26 hours	25–50 mg[b]	5–7
Fluvoxamine	Luvox	OCD	50–200 twice a day[a] Maximum: 200 mg/day up to 11 years and 300 mg/day >11 years	15 hours	25–50 mg[b]	5–7
Paroxetine hydrochloride	Paxil	None	10–40[a]	21 hours	5–10 mg[b]	5–10
Citalopram hydrobromide	Celexa	None	10–40[a]	36 hours	10–20 mg[b]	7
Escitalopram oxalate	Lexapro	Depression	5–20[a]	27–32 hours	5–10 mg[b]	7

Abbreviations: FDA, US Food and Drug Administration; OCD, obsessive-compulsive disorder.

[a] Recommend decreasing the maximum dosage by approximately one-third for prepubertal children.

[b] Recommend using lower dose but in increased increments for younger children.

metabolized via this pathway is necessary. Reduced metabolism of SSRIs may result in *serotonin syndrome*, a relatively rare response to a flood of serotonin, presenting with confusion, restlessness, diaphoresis, shivering, tremor, hyperreflexia, and diarrhea. This syndrome often goes unrecognized, and affected patients may find their way to a pediatrician's office or emergency department. Occasionally, the combination of an SSRI with other prescribed or over-the-counter serotonin-enhancing agents may precipitate such a response. It is important for the prescribing physician to inquire into the use of additional prescribed or over-the-counter medications and be aware of the potential interactions between all agents.

No specific recommendations exist on dose other than to start low and go slow. It is important to use the full dose range for the medication and wait at least 4 to 6 weeks with each increase in dose. Typically, effects may be noted between 1 and 4 weeks, although often it takes up to 8 to 12 weeks to note effects for anxiety disorders. If an adequate trial of 1 SSRI is unsuccessful, a cross-titration to another SSRI is indicated. Suggested dosage ranges are provided in Table 134.1.

Many children with anxiety or depression go on to experience intermittent exacerbations throughout life. This does not mean that they should remain on these medications forever. It is recommended that physcians periodically discuss the length of trial of medication with patients and their families. Current recommendations support an initial 9- to 12-month treatment period with the SSRI that provided response at the same dose that resulted in remission of symptoms. Generally, taper should be avoided around the time of major transitions or stressors and should take place over months, with close follow-up. Finally, re-recurrence of symptoms may indicate the need for longer-term treatment. Patients with chronic depression and/or with multiple episodes of major depression usually require longer-term therapy.

Selective serotonin reuptake inhibitors are generally well tolerated, with mild transient side effects such as gastrointestinal symptoms, headache, increased motor activity, and insomnia. It is important to monitor patients for less common side effects, such as disinhibition, a phenomenon of increased impulsive behaviors in association with SSRIs that is usually dose related. Individuals with ASD as well as younger children are particularly susceptible to this particular side effect.

A withdrawal phenomenon can occur, especially with sudden discontinuation of SSRIs. This risk is inversely proportional to the drug half-life. For example, paroxetine hydrochloride, which has a short half-life, tends to be associated with a far greater risk of withdrawal symptoms than an agent with a longer half-life, such as fluoxetine. Antidepressant discontinuation syndrome may present as flu-like symptoms, including vomiting, diarrhea, and body aches. Simply readministering the skipped dose and tapering off over the course of 1 or 2 weeks alleviates symptomatology.

These medications are controversial. In 2004, the FDA created a black box warning advising that children and adolescents on SSRIs should be monitored for worsening depression, agitation, and suicidality, particularly in the early stages of treatment. This warning arose from an FDA meta-analysis that showed an increased risk of suicidal ideation in depressed teenagers soon after starting the medications. No completed suicides occurred. This prompted an FDA recommendation that children placed on SSRIs be seen weekly for 1 month, then semimonthly for 1 month, then monthly, and, ultimately, at longer regular intervals. The FDA subsequently acknowledged that untreated depression also carries an increased risk of suicide. The potential for benefit usually outweighs the risks, and concerns about suicidal ideation should not detract from the importance of these medications or their judicial use.

The FDA warning led to a decrease in prescriptions of SSRIs, which resulted in the first increase in the suicide rate since the FDA SSRI approval. The FDA warnings should serve only to increase awareness, not serve as a contraindication. An increase in suicidality has not been noted in adolescents with isolated anxiety or ASD. Selective serotonin reuptake inhibitors serve a vital role in helping children paralyzed by anxiety, obsession, and depression to lead more normal lives.

Atypical Antipsychotics (Serotonin-Dopamine Antagonists)

Atypical antipsychotics or second-generation antipsychotics, also known as SDAs, are medications with dopamine D2 and 5-hydroxytryptamine (serotonin) type 2 antagonism (Table 134.2). Compared with conventional antipsychotics, these newer medications offer a reducecd risk of extrapyramidal effects, such as dystonia; *akathisia*, a subjective feeling of restlessness; tremor; tardive dyskinesia; and hyperprolactinemia. These medications carry significant cardiometabolic risks, however. Although initially billed as a safer alternative to traditional antipsychotics, some experts have suggested that these newer medications merely substitute 1 set of severe side effects for another. These medications offer benefits for severe behaviors that are not responsive to other intervention.

Although often used off-label, second-generation antipsychotics are incorporated into best practice clinical guidelines for psychotic depression, schizophrenia, bipolar disorder, agitation in intellectual disability, Tourette syndrome, stuttering, and ASD. The only diagnoses for which an atypical antipsychotic has pediatric approval are schizophrenia, bipolar disorder, mania, and agitation associated with ASD. Therefore, although these medications often lack sufficient empiric evidence to be validated for all the indications mentioned, clinical consensus by experts recommends judicious use in treating children with serious mental illness after other forms of intervention have been unsuccessful or in cases of psychosis or severe aggression. These medications should not be used to promote weight gain, as a sedative or sleep aid, or as a treatment for ADHD.

Medications are chosen based on clinical experience and side-effect profile. Atypical antipsychotics are not innocuous; they must be used with full disclosure to parents. The most common side effects are listed in Box 134.2. The severity of some of the side

Table 134.2. Serotonin-Dopamine Antagonists (Atypical Antipsychotics)

Generic	*Trade Name*	*FDA Pediatric Approval*	*Usual Starting Dose*	*Dose*
Risperidone	Risperdal	Agitation with ASD, schizophrenia, mania, and bipolar disorder	0.25 mg nightly at bedtime	0.25–6 mg/day
Olanzapine	Zyprexa	Bipolar mania and schizophrenia	2.5 mg nightly at bedtime	2.5–20 mg/day
Quetiapine fumarate	Seroquel	Bipolar mania	25 mg twice a day	12.5–400 mg twice a day
Ziprasidone hydrochloride	Geodon	None	20 mg twice a day	20–160 mg/day
Aripiprazole	Abilify	Agitation with ASD, schizophrenia, mania, and bipolar disorder	2 mg once a day	0.5–30 mg/day
Lurasidone	Latuda	Bipolar depression	20 mg once a day	20–80 mg/day

Abbreviations: ASD, autism spectrum disorder; FDA, US Food and Drug Administration.

effects deserves discussion with the parents and patient. With the possible exception of aripiprazole, the SDAs have caused significant increases in weight, glucose, and lipids and decreases in sensitivity to insulin, otherwise known as *metabolic syndrome.*

Transient elevations of prolactin have occurred among recipients of these medications, most commonly with risperidone. The clinical significance of this increase is unclear. Prolonged QT syndrome on ECG is rarely noted, with the exception of ziprasidone hydrochloride. Prolonged QT syndrome on ECG has not been associated with death but remains a clinical concern.

Risperidone is the best studied medication of its class for children. The studies on which its FDA approvals hinged exposed side effects, however, most notably weight gain. Therefore, anticipatory counseling on diet management is routinely recommended. Another important finding indicated that a small but significant number of children with agitation and ASD were successfully able to stop treatment after 6 months, which suggests that a trial off medication may be warranted in those patients with agitation and ASD successfully treated for 6 months.

Box 134.2. Serotonin-Dopamine Antagonists: Potential Side Effects

- Weight gain
- Sedation
- Dizziness
- Hypotension
- Long QT syndrome
- Metabolic syndrome (hyperglycemia and increased lipids)
- Constipation
- Reduced blood cell count
- Dry mouth
- Headache
- Increased liver function tests
- Decreased triiodothyronine, thyroxine
- Extrapyramidal effects
- Akathisia (ie, sense of restlessness)
- Cataracts (in dogs)
- Neuroleptic malignant syndrome
- Tardive dyskinesia

Neuroleptic malignant syndrome is a rare, potentially life-threatening complication of neuroleptic agents that is extremely unlikely with the newer generation of medication. It is important to review the risk of neuroleptic malignant syndrome before starting medication. *Neuroleptic malignant syndrome* is characterized by hyperthermia, autonomic instability, diaphoresis, lead pipe rigidity, increased creatine phosphokinase caused by rhabdomyolysis, and delirium. It may occur at any point during treatment with these medications. Another important side effect to discuss is the risk of tardive dyskinesia with these agents. Although the condition is rare, monitoring is recommended using the abnormal involuntary movement scale (AIMS) at baseline and every 6 months. Risk of tardive dyskinesia increases with duration of use, and after it manifests it may be irreversible in 50% of patients. It is also necessary to explain the risk of dystonia to the families and the use of diphenhydramine as an antidote.

It is important to monitor side effects following the initiation of treatment with an atypical antipsychotic. Recommendations include following body mass index at each visit, after 6 weeks, and again every 9 to 12 months thereafter, as well as checking the following blood chemistries every 6 months: complete blood cell count, a comprehensive chemistry including hemoglobin A_{1c}, prolactin level, fasting blood glucose, and lipid levels. Complete blood cell count with differential can be obtained after a few months after initiation to identify suppression, if any, following treatment. An ECG before starting medications, 1 month after baseline, and biannually are necessary only for children on ziprasidone hydrochloride to monitor the QT interval.

As with any medication, psychotropic agents sometimes are incorrectly prescribed. Generally, however, psychopharmacologic agents remain underused in the management of many disorders. Incorporation for routine screening procedures, such as rating scales for depression and anxiety, can help in early identification of psychiatric conditions, which can result in early intervention for these chronic and disabling disorders. It is hoped that new and ongoing research will help physicians recognize mental illness in children and substantiate and refine the use of such medications in their care.

Careful thought and discussion of target symptoms as well as side effects will help physicians choose the best medication and treatment plan. It will also prepare parents or caregivers to observe the positive and negative responses to medication.

Although this chapter provides substantial detail on side effects, it is critical to understand that the diseases being managed often are incapacitating. Informed consent and parent/caregiver and child involvement are vital in medication choice. Pediatricians have an extremely influential voice in supporting compliance. Therefore, knowledgeable guidance is crucial in helping parents and caregivers make an uncomfortable and difficult decision that may ultimately result in dramatic improvements in their and their child's quality of life.

CASE RESOLUTION

You empathize with the mother about this decision but explain that this medication is a reasonable and safe one to try. The patient starts the medication and experiences some nausea in the first few days. With your reassurance, this resolves. The patient's mother calls a few weeks later to thank you for your advice and to let you know that although her daughter still has difficulties related to the ASD, she seems to be somewhat less anxious and is functioning better at school.

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PART 13

Dermatologic Disorders

CHAPTER 135

Acne

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CASE STUDY

A 15-year-old boy comes to your office for a sports preparticipation physical evaluation. He is healthy and has no questions, complaints, or concerns.

The adolescent is well developed and well nourished, with normal vital signs, including blood pressure. The physical examination is entirely normal except for the skin. Multiple closed comedones are noted along the hairline. Erythematous papules and pustules are present across the forehead and over both cheeks. Scattered open comedones are located over the nose and cheeks as well. The chest and back are clear, with no lesions.

Questions

1. Who gets acne?
2. What are some contributing factors in the development of acne?
3. What is the pathogenesis of acne vulgaris?
4. What are the different types of acne lesions?
5. What management options are available for the treatment of mild, moderate, and severe acne?
6. What are the indications for the use of isotretinoin?
7. What is the prognosis for adolescent patients with acne?

Acne vulgaris is a common chronic inflammatory skin disease that most frequently occurs in adolescents. The spectrum of disease can vary widely, but regardless of type and severity, acne can be severely distressing for patients. The psychological burden and negative effect on quality of life can be comparable to those with asthma, arthritis, or epilepsy. Primary care physicians should, therefore, acknowledge acne as a significant chronic medical problem and treat the condition early and aggressively to prevent permanent sequelae, such as scarring.

Epidemiology

Estimates indicate that more than 85% of people in the United States have been affected by acne and that more than $2 billion is spent annually on acne treatments. Acne most commonly occurs in individuals 9 to 24 years of age, with peak prevalence and severity during puberty. However, the condition can also affect neonates, young infants, and older adults (up to 26% of women and 12% of men). Preteens are more likely to experience comedonal lesions, with progression to more inflammatory lesions during the teenage years. The condition is usually more severe in males but typically lasts longer in females. Certain individuals may be genetically susceptible to acne. White teenagers are more likely to have acne than black, Hispanic, or Asian teenagers. However, patients with darker skin tones often have more issues with post-inflammatory discoloration and scarring.

Etiology

Acne has a complex, multifactorial etiology with many overlapping influences that are endogenous and exogenous (Box 135.1).

Internal (host) factors include hormones (eg, androgen excess, changes in estrogen or progesterone during menses, stress-induced cortisol release), skin microflora balance (especially with *Cutibacterium* [previously *Propionibacterium*] *acnes*), sebum overproduction, skin hyperkeratinization, and stimulation of internal inflammatory pathways.

External factors include medications and drugs (ie, progestin-only contraceptives, isoniazid, phenytoin, corticosteroids, anabolic steroids, and lithium-containing compounds), chemicals (ie, petroleum), oil- or wax-containing hair care products and cosmetics, overzealous facial cleansing, local skin occlusion from sports gear and excessive perspiration, and diet. While specific foods such as chocolate, caffeinated drinks, and fried or greasy foods have not been shown to directly cause or worsen acne, emerging research suggests that diets with high-glycemic indices or high dairy intake

Box 135.1. Factors Contributing to Acne

Endogenous (Internal [Host]) Factors

- Skin microflora imbalance
- Sebum overproduction
- Hyperkeratinization
- Pro-inflammation pathways
- Hormonal imbalances

Exogenous (External) Factors

- Medications/drugs
- Oily/waxy hair products and cosmetics
- Excessive face washing/scrubbing
- Excessive sweating
- Occlusion (eg, hats, headbands, sports gear)
- Diet (eg, high glycemic load, high diary intake)

may contribute to inflammation and the development of acne lesions.

Pathophysiology

The pathogenesis of acne involves 4 major interrelated processes that naturally occur within the pilosebaceous unit: hyperkeratinization of follicular infundibulum, sebaceous gland overproduction and alteration of sebum composition, proliferation of *C acnes*, and immune response and inflammation (Box 135.2). Alteration or imbalance of any of these 4 normal processes can lead to formation of acne lesions.

Hyperkeratinization of Follicular Infundibulum

Keratinocytes constitute 90% of the cells of the epidermis and function to produce a keratin barrier that protects against environmental damage. Activation of the innate immune system by internal or external factors will initiate pro-inflammatory biochemical cascades. One important pathway includes activation of toll-like receptors (TLR-2/4) and ensuing release of defensin and interleukin. Interleukin-1α specifically has been linked to increased keratinocyte proliferation, which, in turn, leads to overproduction of keratin and reduced desquamation and remodeling within the pilosebaceous unit. This results in the formation of a keratin plug within the follicular infundibulum. Keratin plugging leads to retention of sebum and cellular debris and subsequent development of the microcomedo, the earliest precursor lesion of acne.

Sebaceous Gland Overproduction and Alteration of Sebum Composition

Sebum is a complex mixture of oils that includes triglyceride and fatty acid breakdown products, wax esters, squalene, and cholesterol. Any alteration to the composition of these different lipids can contribute to acne lesion formation. A common cause of alteration is antioxidant and free radical imbalance. Exposure to pollution and UV radiation decrease skin antioxidants, such as vitamin E, and can lead to formation of reactive oxygen species. Increases in reactive oxygen species lead to subsequent oxidization of sebum lipids and inflammation that contribute to acne.

The amount of sebum produced is also important, because overproduction can contribute to inflammation and comedo formation. The sebaceous gland is highly sensitive to hormonal stimulation, especially the increase in androgens during puberty and corticotrophin-releasing hormone spikes during stress. Hormonal activation causes sebaceous glands to undergo hypertrophy, leading to an overall increase in sebum production. Diet can also lead to increase in sebum production via activation of insulinlike growth factor 1, leptin, and peroxisome proliferator-activated receptors (PPARα, β, and γ). Alternatively, activated retinoic acid and retinoid-X receptors have an antiproliferative effect on keratinocytes and inhibit lipid synthesis.

Box 135.2. Acne Pathogenesis

- Hyperkeratinization leads to pilosebaceous follicle plugging and microcomedo formation.
- Hormones induce sebum overproduction and lead to over-proliferation of *Cutibacterium acnes*.
- *C acnes* leads to increased inflammation and innate immune response.
- Ongoing innate immune responses attract inflammatory cells and damage the dermal matrix.

Proliferation of *Cutibacterium Acnes*

Cutibacterium acnes is a gram-positive anaerobic diphtheroid bacterium that plays a major role in acne pathogenesis. *Cutibacterium acnes* normally exists in balance alongside *Staphylococcus epidermidis* as the predominant cutaneous microflora of the sebaceous follicle. In the setting of normal microflora balance, *C acnes* limits proliferation of *Staphylococcus aureus* and *Streptococcus* species, whereas *S epidermidis* helps limit proliferation of *C acnes*. When left unchecked, *C acnes* releases hyaluronate lyase and CAMP (Christie Atkins Munch Petersen, the researchers who discovered the factor) factors that cause extracellular matrix degradation and porphyrins that oxidize sebum, and can form a strong antibiotic resistant biofilm—all of which lead to inflammation that can cause acne.

Immune Response and Inflammation

The innate immune system also plays a key role in acne lesion formation and subsequent scarring. Innate immune responses release inflammatory mediators that activate the hyperkeratinization that causes keratin plugging, which, in turn, leads to the rupture of the pilosebaceous follicle and expulsion of follicular contents into the dermal layer of skin. This spillage of sebum, keratin, and bacteria leads to further inflammation and the development of inflammatory acne lesions. In addition, specific cytokines such as interleukin-8/10 also attract circulating inflammatory cells into the tissue and promote pustular acne lesions. Many inflammatory cytokines can also induce matrix metalloproteinases (eg, MMP-9) that cause dermal matrix destruction and subsequent scar formation.

Clinical Presentation

The lesions of acne primarily affect the face, especially central facial areas, or the T-zone, which includes the forehead, nose, and chin. Lesions can also be found on other areas of the body that are dense in sebaceous glands, including the neck, chest, shoulders, and back.

There are a number of different types of acne lesions (Box 135.3). Lesions are typically described as comedonal (non-inflamed) or inflammatory. Comedones can be open or closed to the environment. *Closed comedones*, or *whiteheads*, are small, flesh-colored bumps with no surrounding erythema that are caused by plugging of the sebaceous follicle and resultant dilation that is closed to the surface of the skin. *Open comedones*, or *blackheads*, are small, dome-shaped papules with an open orifice that contains central dark material. These also occur as a result of dilatation of the follicular orifice but are open to the outside environment. The dark-colored material at the surface of the skin within open comedones is not dirt;

Box 135.3. Acne Characteristics

- Located on face, chest, back, and shoulders.
- Comedones are non-inflamed, open (blackheads), or closed (whiteheads).
- Inflammatory lesions—papules, pustules, or nodules.
- Nodules can be large, deep, and cystic.

therefore, patients should not attempt to scrub off or pick out the lesion. The dark color is actually caused by a number of processes, including melanin deposition in the horny cells, interference with the transmission of light through compacted epithelial cells, and oxidation of keratin and sebum.

Pustules and papules are inflammatory lesions. Pustules lie in the superficial epidermal layer of the skin, and papules form in the lower dermal layer. Because of their deeper location, papules are often accompanied by a more severe inflammatory reaction, and scarring may result. Nodules or cysts are suppurative inflammatory lesions located deep within the dermis. Associated with the most severe form of acne, nodules are the result of deep papules that suppurate and rupture, and then subsequently become lined with epithelium to form cysts.

Evaluation

History

A detailed history investigating the medical and psychosocial aspects of acne is key (Box 135.4). It is often helpful to start with the psychological effects first. How do patients feel about their acne and how does it affect their life? Do they desire treatment at this time, and if so, what are their expectations about treatment and recovery? From a medical standpoint, the health professional should determine how long the acne has been present, the types of lesions that are present, if and how the condition has ever been treated, and what has or has not worked in the past. A general review of systems is important to exclude symptoms associated with androgen excess or other metabolic disorders that may be contributing to acne breakouts.

Physical Examination

The physical examination should focus on the primary sites of acne—face, chest, back, and shoulders—although the entire skin should be inspected closely at the first visit. Currently no universally accepted grading scale for acne severity exists. However, American Academy of Dermatology guidelines currently use the number of lesions and extent of inflammation as the main factors to determine severity (Table 135.1). The presence of nodular lesions is of particular importance, because this indicates more severe acne even in the absence of other lesions and typically requires systemic treatment. The presence and extent of scarring should also be assessed as a possible predictor of outcome.

A complete physical examination at the initial visit is important to assess for signs of hormonal imbalance that may be contributing to symptoms. Androgen excess can present with hirsutism, male pattern baldness, obesity, and acanthosis nigricans. Indications of virilization, such as congenital adrenal hyperplasia or androgen-producing tumors, have more severe effects, such as clitoromegaly, loss of female body contour, and deepening of the voice. Signs of steroid use or cortisol excess include central obesity, moon facies, stretch marks, buffalo hump, and decreased testicular volume in males. Acne in prepubescent children older than 1 year is never normal and is cause for concern for precocious puberty and hormone-secreting tumors. Signs include axillary and pubic hair, breast development in females, and testicular enlargement in males.

Box 135.4. What to Ask

Acne

Psychological Aspects

- Is the patient bothered or embarrassed by the lesions?
- Do the patient's feelings about the acne prevent him from participating in certain activities?
- Is the patient bullied by the patient's peers because of the acne?
- Does the patient desire treatment at this time?
- What are the patient's expectations for treatment and resolution?
- Is there any past history of psychiatric conditions, such as depression or anxiety?

Personal Acne History

- How long have the lesions been present?
- Where on the patient's face or body do breakouts usually occur?
- What types of acne lesions does the patient usually have?
- Does the patient pick at or try to pop the lesions?
- Do specific activities, medications, or environmental factors seem to make the acne worse?
- Are timing factors, such as menses or stress, related to breakouts?

Acne Treatment History

- Has the adolescent ever received treatment for acne in the past?
- Did the patient try self-treatment only with over-the-counter products, or was therapy prescribed by a physician?
- What specific treatments were used?
- How long did treatment continue?
- What treatments seem to help or worsen the acne?
- If the patient stopped any treatments, what were the reasons the therapy was discontinued?

Related History

- Does the adolescent have any other medical conditions?
- Is the adolescent taking any medications? Any history of steroid use? If female, any use of hormonal contraception?
- Is there a family history of acne with or without scarring?

Reactive Oxygen Species Screening

- Full 10-system review of systems at the initial encounter with subsequent focused check-ins.
- If female, are menses regular? Is there a history of hirsutism, male pattern baldness, or voice deepening?
- If prepubescent, are there any signs of precocious puberty?

Laboratory Tests

In general, no laboratory studies are needed at the time of the initial evaluation. However, targeted testing is warranted if there is concerning

Table 135.1. Classification of Acne	
Category	*Physical Findings*
Grade 1 Mild comedonal	A few non-inflammatory lesions (ie, open and closed comedones) with no more than 1 small inflammatory lesion
Grade 2 Mild inflammatory	Some non-inflammatory lesions with no more than a few inflammatory lesions
Grade 3 Moderate	Many non-inflammatory lesions and/or some inflammatory lesions, with no more than 1 small nodular lesion
Grade 4 Severe	Many non-inflammatory lesions and/or inflammatory lesions, with no more than a few nodular lesions
Grade 5 Very severe	More than a few nodular lesions regardless of number of non-nodular lesions

history or examination findings that are suggestive of a hormonal abnormality. In females with signs of androgen excess, initial studies should include testosterone, dehydroepiandrosterone sulfate, androstenedione, follicle-stimulating hormone, and luteinizing hormone levels. Additional supplemental testing for prolactin, estradiol, and sex-hormone-binding globulin levels may be included. Screening for Cushing syndrome should begin with corticotropin and early morning cortisol levels. Any evidence of precocious puberty should prompt bone-age imaging and testing for follicle-stimulating hormone, luteinizing hormone, testosterone, dehydroepiandrosterone sulfate, insulinlike growth factor 1, and thyrotropin levels. If any abnormality is found, prompt referral to an endocrinologist is needed.

When isotretinoin is indicated, several pretreatment studies are necessary, including a complete blood cell count, liver function tests, and a fasting lipid profile. In addition, 2 negative pregnancy tests 1 month apart are required prior to and within 2 weeks of starting isotretinoin in female adolescents. These studies should be obtained in consultation with a dermatologist, who is generally responsible for prescribing isotretinoin through the iPLEDGE program (see the Isotretinoin Therapy section).

Management

The general management of acne begins with counseling. The health professional should start by providing a general, nontechnical overview of the pathophysiology of acne and eliciting any related questions. Common therapy options should be discussed while exploring possible barriers to treatment to individualize therapy for optimized adherence and efficacy (Box 135.5). Common barriers include patient motivation and maturity, unrealistic expectations of therapy duration and likely outcome, complexity of treatment regimen, medication-related side effects, and overall cost to families. Increased parental involvement can help mitigate some of these barriers, particularly when the patient is young or has severe acne requiring a more complex treatment regimen.

Prior to starting treatment for acne, physicians should counsel the patient and family that acne often appears to worsen with treatment for the first 2 to 4 weeks. Noticeable improvement of acne from any treatment regimen usually takes at least 4 to 8 weeks. Patients should be reminded that treatment is long-term, because medications only control the acne but do not cure it.

The specific therapies prescribed depend on the severity of the acne, the type of lesions present, and the patient's ability to adhere to the proposed treatment (Table 135.2). The most common regimens

Box 135.5. General Management Recommendations

- Wash skin with a mild soap-free cleanser and water no more than 1–2 times per day.
- Avoid antibacterial washes (other than benzoyl peroxide) because they may lead to bacterial resistance.
- Use cosmetics and moisturizers that are oil free and noncomedogenic.
- Use sunscreen daily; most acne medications are photosensitizing and increase UV damage.
- Avoid picking at lesions and excessive scrubbing, especially with abrasive cleansers or exfoliators.
- Maintain a healthy diet; a low-fat, low-glycemic diet may be more helpful for patients who have obesity.
- Follow the prescribed regimen carefully, because adherence is key to treatment success.
- Manage medication-related side effects, such as increased redness and dryness of the skin.
- Understand that long-term treatment is often required.

Table 135.2. Treatment of Acne	
Classification	*Recommended Treatment Regimen*
Grade 1 Mild comedonal	First-line: topical retinoid monotherapy, starting every other day. Second-line: increase to daily use and/or add benzoyl peroxide.
Grade 2 Mild inflammatory	First-line: topical retinoid or benzoyl peroxide monotherapy, starting every other day. Second-line: increase to daily use and/or add benzoyl peroxide/topical retinoid. Third-line: add topical antibiotic once or twice daily.
Grade 3 Moderate	First-line: topical retinoid and benzoyl peroxide double therapy daily. Second-line: add topical antibiotic once or twice daily. Third-line: trial of oral antibiotics (especially if body acne present). Adjuncts: if female, can add oral contraceptives or spironolactone. Recalcitrant: isotretinoin.
Grade 4 Severe	First-line: topical retinoid, benzoyl peroxide, and topical antibiotic triple therapy daily. Second-line: isotretinoin. Adjuncts: trial of oral antibiotics; if female, oral contraceptives or spironolactone.
Grade 5 Very severe	First-line: isotretinoin (and oral contraceptives, if female). Adjuncts: intralesional steroids or oral steroid taper, oral antibiotics.

include topical products such as retinoids and benzoyl peroxide, which can be used alone or in combination with each other as well as with topical or oral antibiotics, hormonal agents, and isotretinoin. Regardless of regimen selection, close follow-up is needed for subsequent titration or modification of the treatment regimen according to the patient's clinical response, adverse effects experienced, and overall adherence to treatment.

The patient's skin type should also be taken into consideration when selecting the appropriate vehicle for the active ingredient. Most topical medication comes in a variety of forms, including creams, gels, ointments, foams, and lotions. Oily skin types tend to respond better to gels, foams, or solutions, whereas lotions, creams, and ointments are better suited for dry skin.

Topical Therapy

Topical retinoids are vitamin A derivatives that treat existing acne lesions (comedolytic) and prevent the formation of new microcomedones. The mechanisms of action include normalizing follicular keratinization, decreasing the adhesiveness of horny cells shed into the follicular lumen, and reducing inflammation.

Topical retinoids are now recommended as first-line treatment for comedonal and inflammatory acne. They can be used alone as monotherapy for mild acne or as part of a combination regimen for moderate and severe acne. Several different formulations of topical retinoids are available in a wide variety of concentrations and vehicles.

- Tretinoin (eg, Retin-A, Avita, Atralin) is the most widely used topical retinoid and is available only by prescription. It comes as a gel, cream, or liquid in concentrations varying from 0.025% to 0.1%. Newer microsphere vehicle technology (eg, Retin-A Micro) is less irritating and allows delivery of the medication more slowly over time to decrease side effects without compromising effectiveness.
- Adapalene (eg, Differin) is a newer third-generation retinoid that is less irritating and more photostable than other topical retinoids. It is also the only topical retinoid that is currently available without a prescription. The 0.1% gel is available for purchase over the counter, whereas the 0.1% cream/lotion and 0.3% gel are still prescription only. It is not approved for children younger than 12 years.
- Tazarotene (eg, Tazorac) is another newer third-generation topical retinoid that was originally created for the treatment of psoriasis. It is the most effective of the topical retinoids; however, it is also significantly more expensive and has a higher adverse effect profile than other topical retinoids, including teratogenicity (pregnancy category X). For these reasons it is not widely used in the treatment of acne.

Retinoids are frequently used as part of combination therapy with benzoyl peroxide, but they cannot be applied simultaneously. Benzoyl peroxide causes inactivation of the topical retinoid when they are applied together. Most health professionals recommend applying benzoyl peroxide in the morning and topical retinoids at night. Another reason for nightly usage is that retinoids are photolabile and degrade quickly when exposed to sunlight, thus significantly decreasing their effectiveness.

Common dose-dependent side effects are redness, dryness, peeling, stinging, and burning of the skin. To minimize these effects, only the lowest concentration clinically indicated should be used. Skin type should also be considered, and a history of sensitive or dry skin may necessitate initial use only every 2 to 3 days. Correct application and use of moisturizers can also help prevent side effects and should be discussed when initially prescribed. Application should ideally occur 20 to 30 minutes after the skin is cleansed and completely dried. A pea-sized amount should be gently spread as a thin, even layer over the entire face, followed by a noncomedogenic moisturizer. Retinoids also cause significant photosensitivity of the skin; therefore, use of sun protection factor 30 or higher sunscreen should be strongly recommended, and excessive sun exposure or tanning should be strongly discouraged.

Benzoyl peroxide is another commonly used topical medication that helps to treat acne in several ways. Similar to topical retinoids, benzoyl peroxide is also comedolytic and anti-inflammatory. What makes it unique from other treatment options is that it is the only medication with antibacterial properties against *C acnes* with no reported resistance. In fact, it is recommended to use benzoyl peroxide when traditional antibiotics are used as part of an acne treatment regimen to prevent the development of antibiotic resistance.

Benzoyl peroxide can be used as first-line monotherapy for mild inflammatory acne and is often used in combination regimens for comedonal acne and more severe acne cases. It is typically available in concentrations of 2.5%, 5%, and 10% as cream, gel, or body wash. All strengths are available over the counter and are relatively inexpensive.

The health professional should keep in mind when choosing a benzoyl peroxide concentration that a higher concentration does not always equate to higher efficacy and may only result in a higher level of adverse effects. Common side effects of benzoyl peroxide are generally the same as those of topical retinoids and additive when used in combinations and higher strengths. It is, therefore, recommended to start with the lowest concentration of benzoyl peroxide indicated (2.5%–5% for the face; 5%–10% for the body) and to initiate gradually over time. Initially, a thin application should be used once every other day, and the frequency and/or strength can be increased as tolerated.

A serious adverse effect is allergic contact dermatitis. This manifests as an erythematous and very pruritic papular-vesicular eruption on areas of application. While it rarely develops, its presence necessitates immediate discontinuation of all benzoyl peroxide-containing medications.

One additional issue to be aware of is that benzoyl peroxide has a significant bleaching effect on textiles. This can lead to splotchy, orange-yellow discoloration of towels, bed linens, and clothing if patients are not appropriately counseled. There are linens that are specifically marked as benzoyl peroxide resistant.

Salicylic acid is a compound originally produced from willow tree bark (like aspirin) and has comedolytic effects when applied to skin. It is available in concentrations ranging from 0.5% to 2% and comes in a variety of vehicles. It is the main active ingredient in many over-the-counter facial cleansers and "spot-treatment" serums marketed for the treatment of acne. However, there are limited data to support its effectiveness. It is, therefore, not included in most acne treatment

algorithms or physician-prescribed regimens. Patients should be advised to check labels on over-the-counter products, because concurrent use of salicylic acid-containing products with other topical medications can cause worsening of redness, dryness, burning, and peeling.

Antibiotic Therapy

Antibiotics can be used as adjuncts in the treatment of inflammatory acne of all severities. The choices of topical versus oral and which specific antibiotic to use typically depend on the extent of skin involvement and severity of inflammation. However, any antibiotics chosen (whether topical or oral) should not be used as monotherapy or first-line therapy, or for continuous periods longer than 3 to 4 months, because of the risk of inducing bacterial resistance. It is recommended to use benzoyl peroxide alongside any antibiotics and to begin tapering usage after 6 to 8 weeks of treatment to help prevent development of resistance.

Topical antibiotics are often helpful as second-line therapy for mild to moderate inflammatory acne that is unresponsive to topical retinoids and/or benzoyl peroxide. Local side effects are generally similar to other topical acne medications, and systemic adverse effects are significantly less frequent than with oral counterparts because of minimal systemic absorption. Allergic reactions to topical antibiotics are rare and are typically limited to localized dermatitis.

- Clindamycin and erythromycin are the most popular topical antibiotics. Clindamycin is available by prescription as a 1% gel and is now is the preferred first-choice topical antibiotic because of its superior efficacy. Erythromycin is available as a 2% gel by prescription. Both are also available as fixed-strength combination preparations with benzoyl peroxide. Although these combination preparations are generally more costly, overall adherence often improves due to reduced regimen complexity. Topical antibiotics and combination preparations can be used once or twice daily.
- Dapsone (eg, Aczone) is a sulfa-containing antibiotic that is typically used in its oral formulation to treat leprosy. However, the topical form of the drug can be used in combination regimens to treat severe or nodulocystic acne or as second- or third-line therapy for resistant mild to moderate acne. It is available by prescription as a 5% gel that can be used once or twice daily. Dapsone gel should not be co-applied with benzoyl peroxide because this will cause orange-brown discoloration over the skin (however, this discoloration can be washed off). It should also not be used in patients who are taking oral dapsone or antimalarial drugs because of the potential for severe hemolytic reactions. However, hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency have *not* been reported when using topical dapsone alone; therefore, glucose-6-phosphate dehydrogenase testing is *not* required prior to starting treatment. More common side effects include redness, dryness, and peeling of the skin.

Systemic oral antibiotics are most often used for inflammatory acne that is severe refractory or that covers large areas of the trunk. It should be noted that oral antibiotics have not been shown to be effective against comedonal acne. Oral antimicrobial therapies help inhibit over-proliferation of *C acnes*, which, in turn, limits sebum oxidation and additional cellular matrix damage. As a result, lesser amounts of free fatty acids and other by-products are released, leading to decreased levels of inflammation.

The ultimate goal of oral antibiotic therapy is use of the lowest dose indicated to control lesions and minimize side effects. However, most patients require prolonged or frequent intermittent courses of oral antibiotics before remission occurs. Once new inflammatory lesions have stopped emerging (usually after 6–8 weeks), the dose of the oral antibiotic may be gradually tapered over 1 to 2 months and topical antibiotic treatment may be substituted.

- Tetracycline and its derivatives (ie, minocycline, doxycycline, and sarecycline) have been found to be the most effective and should be considered the first-line choices among the systemic antibiotics. Currently, extended-release minocycline and sarecycline are US Food and Drug Administration (FDA) approved for treatment of moderate to severe inflammatory acne in children 12 years and older and 9 years and older, respectively.
- Azithromycin, trimethoprim-sulfamethoxazole, amoxicillin, and cephalexin are significantly less effective and generally are not useful choices unless patients have contraindications to tetracyclines. Common contraindications to tetracyclines include age younger than 8 years and active pregnancy.
- Erythromycin is not recommended because of rising bacterial resistance.
- Clindamycin is not recommended because of the associated risk of pseudomembranous *Clostridium difficile* colitis with the extended use needed for acne treatment.

The most common side effects of oral antibiotics include candidal vaginitis, especially in females who also take oral contraceptives; gastrointestinal (GI) upset; and photosensitivity. Phototoxicity and pill esophagitis occur most commonly with oral doxycycline; therefore, patients must be instructed to use sunscreen liberally and remain upright for at least 1 hour after taking the medication. Significant rare but serious potential adverse effects associated with the first-line tetracycline class include cholestatic hepatitis (especially if liver dysfunction is already present), hypotension, cardiac arrhythmias (eg, torsades de pointes, ventricular tachycardia), and severe neurologic effects (ie, confusion, psychosis, seizures, and hearing loss).

Hormonal Therapy

Hormonal therapies are very helpful adjunct treatments for menstruating females with moderate to severe acne and signs of androgen excess. They work via a variety of mechanisms to decrease or inhibit androgen overproduction, which often contributes to acne. Several different medications with antiandrogen effects are available.

Oral contraceptives treat hyperandrogenism by blocking androgen synthesis and activity. They decrease androgen production through negative feedback inhibition of pituitary gonadotropin secretion and direct suppression of 5a-reductase. They decrease the effect of androgens directly, by blocking the testosterone receptor, as well as indirectly, by increasing sex-hormone-binding globulin to limit active free testosterone. In general, oral contraceptives must be taken for 3 to 4 months before improvement is seen, with relapses occurring if treatment is discontinued. Maximum effects are usually seen by 6 months of usage. It should also be noted that a

Papanicolaou test and a bimanual pelvic examination are *no longer indicated* before initiating the use of an oral contraceptive.

There are currently 4 FDA-approved combined oral contraceptives specifically for the treatment of acne:

- Ethinyl estradiol and norgestimate (eg, Ortho Tri-Cyclen)
- Ethinyl estradiol and norethindrone acetate with ferrous fumarate (eg, Loestrin)
- Ethinyl estradiol and drospirenone (eg, Yaz, Yasmin, Ocella)
- Ethinyl estradiol and drospirenone with levomefolate (eg, Beyaz, Safyral)

When choosing an oral contraceptive for acne treatment, a low-dose combination estrogen-progestin formulation is recommended to help limit possible adverse effects. Unopposed progestin, especially medroxyprogesterone injections (eg, Depo-Provera), can worsen acne and lead to hirsutism. Localized slow-release progestin implants (eg, Nexplanon, Implanon) and intrauterine devices (eg, Mirena, Skyla) are less likely to have these adverse effects. High levels of estrogen may cause nausea, vomiting, bloating, decreased libido, systemic hypertension, and idiopathic intracranial hypertension and increase the risk of deep vein thrombosis and breast or cervical cancer. Alternatively, very low doses of estrogen may not be sufficient for normal bone mass accrual that is critical during adolescence.

Contraindications to oral contraceptives include pregnancy, breastfeeding, significant hypertension (ie, systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg), migraine with aura, heavy smoking, prior deep vein thrombosis or pulmonary embolism, history of stroke or myocardial infarction, or a diagnosis of breast or cervical cancer. Patients should also be warned that efficacy of the oral contraceptive may be affected by other medications, especially rifampin and griseofulvin.

Spironolactone is an aldosterone receptor antagonist normally used as an antihypertensive. However, it also competitively binds the testosterone receptor, thus blocking activity of testosterone and dihydrotestosterone. The combined antihypertensive and antiandrogen effects make it especially helpful for young women with metabolic syndrome and obesity. It should be avoided in young men because of a high likelihood of causing gynecomastia. It is typically dosed from 50 to 200 mg daily and can be tapered once acne improvement is noted. Common side effects include polyuria, hypotension, dizziness, fatigue, headache, and menstrual irregularities. Serious adverse effects are related to hyperkalemia caused by aldosterone blockade. However, potassium levels *do not* need to be checked prior to initiation for most healthy young patients. There are also no data showing increased risk of hyperkalemia when drospirenone oral contraceptives and spironolactone are used together.

Steroid therapy can be useful for the treatment of severe inflammatory acne in boys and girls, especially for those with nodular acne. Deep nodular lesions often respond quickly to the anti-inflammatory effects of intralesional injections of triamcinolone acetonide (eg, Kenalog; 10 mg/mL) and oral prednisone tapers (5–30 mg per day over 5–7 days, with maximum 0.5–1 mg/kg/day over several weeks). However, steroids should never be used topically because they will cause acne to significantly worsen secondary to *C acnes* overgrowth. Long-term use is discouraged given the risks of serious long-term adverse effects.

Isotretinoin Therapy

Isotretinoin (eg, Absorica, Zenatane, Claravis, Amnesteem, Myorisan) is a systemic oral analog of vitamin A and influences nearly all aspects of acne formation: sebum secretion, follicular keratinization, and inflammatory responses. It is the strongest and most effective acne treatment available and is among the few treatments to provide long-term remission. Currently, it is the recommended first-line therapy for very severe (nodulocystic) acne and can be used as second- or third-line therapy for resistant moderate to severe acne. However, given the high incidence of side effects and potential for serious adverse reactions, referral to a dermatologist is strongly recommended for patients who require isotretinoin therapy.

Common side effects include intense dryness of the skin and mucous membranes, myalgias and joint pain, GI upset, fatigue, headache, hematuria, hematologic abnormalities (eg, anemia, neutropenia, thrombocytopenia, thrombocytosis), and elevation of triglycerides and transaminases. Therefore, baseline blood cell counts, liver function tests, and lipid panel tests should be obtained prior to initiation of isotretinoin and monitored regularly for the duration of treatment.

Severe adverse effects include GI hemorrhage, pancreatitis, hepatitis, inflammatory bowel disease, agranulocytosis, allergic vasculitis, stroke, bronchospasm, decreased bone mineral density, rhabdomyolysis, glomerulonephritis, pseudotumor cerebri, optic neuritis, and seizures. Neuropsychiatric effects including depression and suicidal ideation have long been attributed to isotretinoin because of their association to hypervitaminosis A and have led to related black box warnings by the FDA. However, data to support this correlation are limited to case reports and related database reviews. Regardless, given the high likelihood of depressive symptoms in an adolescent with recalcitrant acne, health professionals are advised to be aware of the possible coexistence of a mental health disorder when prescribing isotretinoin and are urged to monitor patients closely for indication for psychiatric referral.

Teratogenicity is also a significant concern for adolescent and adult women taking isotretinoin. To minimize fetal exposure to isotretinoin, the FDA implemented a mandated distribution program called iPLEDGE in 2007 to register all patients and their prescribing physicians, along with distributing pharmacies and manufacturers. iPLEDGE is a computer-based risk management program that requires prescribers to read and sign designated policies and procedures and patients to read educational material and sign an informed consent. Additionally, documentation of 2 negative pregnancy tests separated by 1 month and 2 forms of active birth control are required prior to dispensing the medication to patients. An identifying qualification sticker must be affixed to all isotretinoin prescriptions indicating the prescribing physician is appropriately registered with the iPLEDGE distribution program. Monthly follow-up and pregnancy testing by the prescribing dermatologist are mandatory.

Prognosis

Most uncomplicated cases of acne (approximately 90%) resolve by the third decade after birth. Hyperpigmentation and scarring are the most common sequelae of acne and affect 40% to 50% of patients.

While they can be more severe and widespread for patients who are severely affected, they can occur even with mild to moderate acne. Therefore, prompt treatment is crucial.

Post-inflammatory hyperpigmentation is a common problem once acne resolves and can sometimes be more upsetting to patients than the acne itself. It is triggered by inflammation within the skin that activates melanocytes to produce excess melanin, thus leading to dark spots. Darker-skinned patients are more commonly affected because of higher baseline melanin production. The most effective preventions are early acne treatment, sunscreen, and avoidance of irritant such as abrasives and exfoliants. One possible treatment for lighter-skinned patients is azelaic acid (eg, Azelex, Azelike), a naturally occurring wheat derivative that treats acne and lightens skin. It is available by prescription as a 20% cream and can be applied once or twice daily.

Atrophic scars develop in areas where there is loss of tissue. The 2 common types of atrophic scars are ice pick and boxcar scars. Ice pick scars are prominent pinpoint holes in the skin. Boxcar scars are depressed rounded areas with steeply angled sides, similar to the punched-out appearance of chickenpox scars. These scars can be treated in a number of ways; however, all treatments are very expensive, may only provide temporary improvement, and come with a risk of infection, worsening hyperpigmentation, prolonged redness, and poor healing—all of which increase with darker skin tones.

Resurfacing involves purposeful injury to the epidermis and superficial dermis to stimulate neocollagenesis and scar repair. Methods include chemical peels, dermabrasion, and laser resurfacing.

Lifting is an attempt to elevate the scar base to match the surrounding tissues. Techniques include injection fillers, subcision, and punch elevation.

Excisional treatments are reserved for deep, sclerotic, or severely hypopigmented scars and include punch or elliptical excision and punch grafting.

Keloid scars are hypertrophic masses of raised tissue on the surface of the skin that form as a result of increased collagen production as acne wounds heal. These scars are incredibly difficult to treat because manipulation of the scar tissue often triggers additional keloid formation and leads to scarring that is often worse than that experienced prior to treatment. The most effective treatment currently available includes cryotherapy followed by intralesional steroid injection to remove scar tissue and attempt to prevent new keloid formation. Additional adjunct therapies are also available but are less effective.

CASE RESOLUTION

The adolescent should be offered treatment for his mild to moderate comedonal and inflammatory acne. This may include benzoyl peroxide, retinoic acid, and topical antibiotics. The common side effects of the medications (eg, dry skin, peeling) should be reviewed, and the teenager should be instructed to use a noncomedogenic sunscreen. A follow-up appointment should be arranged for 4 to 6 weeks after the initiation of treatment to assess adherence to and tolerance of the prescribed treatment regimen and to address any questions or concerns.

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CHAPTER 136

Disorders of the Hair and Scalp

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CASE STUDY

A 6-year-old girl presents with a 1-month history of swelling on the right side of her scalp that is associated with hair loss. She has previously been in good health, and she has no history of fever. On examination, she is afebrile, has normal vital signs, and appears well. A 2- × 2-cm (0.8- × 0.8-in) area of nontender, boggy swelling with associated alopecia is apparent over the scalp in the right temporal area. Small pustular lesions are scattered over the involved area. Generalized scaling of the scalp and occipital adenopathy are evident.

Questions

1. What are the common causes of circumscribed hair loss in children?
2. What are the common causes of diffuse hair loss in children?
3. What are the common causes of scalp scaling in children?
4. What features distinguish tinea capitis from alopecia areata?
5. What is the treatment for tinea capitis? Is there a role for topical antifungal agents?

Disorders of the scalp may be congenital or acquired during childhood or adolescence. Conditions may be further classified according to the presence or absence of hair loss (alopecia), whether the hair loss is diffuse or circumscribed, and whether the hair loss results in scarring of the scalp.

Epidemiology

Scalp Disorders Without Associated Hair Loss

Among the congenital scalp disorders, caput succedaneum and cephalohematoma occur in an estimated of 1% of caesarean sections and 2% of vaginal deliveries via a cephalic position. Neonatal scalp abscess has an prevalence of 0.1% to 5.2%. Meanwhile, 85% of neonatal human herpesvirus infections occur at time of delivery and the scalp usually has the longest contact with the cervix, one of the sites for transmission of infection.

Among acquired scalp disorders, seborrheic dermatitis is most frequently seen in infants; however, it can occur in children and even adults, with an estimated prevalence of 5% across all groups (see Chapter 138). Atopic dermatitis is a common condition, affecting between 10% and 20% of school-age children in the United States (see Chapter 138). The prevalence of head lice (pediculosis capitis) is highest among children aged 3 to 11 years, with a propensity for affecting females and blacks more commonly. Scabies disproportionately affects resource-limited and crowded areas, with an estimated prevalence of 100 million people worldwide.

Scalp Disorders Associated With Hair Loss

Congenital scalp disorders leading to hair loss are uncommon compared with acquired scalp conditions. *Nevus sebaceus* is a congenital hairless lesion that mainly occurs on the face and scalp, occurring in about 3 of 1,000 neonates and affecting males and female newborns equally. *Aplasia cutis congenita*, the congenital absence of skin, presents in approximately 1 in 10,000 births.

Tinea capitis is a common acquired scalp disorder that can be associated with hair loss. Tinea capitis is a fungal infection of the scalp most often caused by the dermatophytes *Microsporum canis* or *Trichophyton tonsurans.* Tinea capitis affects primarily school-age children between the ages of 3 and 7 years and is less common in infants and postpubertal adolescents. Prevalence varies geographically but is estimated to be between 3% and 13% in the pediatric population. Boys are affected more often than girls with *M canis,* although both are affected equally in epidemics caused by *T tonsurans.* Black children have the highest rates of infection, although the reasons for this are unclear. Up to 60% of affected children are asymptomatic.

Alopecia areata is considered an autoimmune disorder targeting the hair follicles, with a prevalence of 0.1% to 0.2% in the United States, occurring equally in males and females. Although alopecia areata may develop at any age, it is rare before the age of 1 year, and 40% to 50% of cases of alopecia areata develop before the age of 21 years.

Traction alopecia is more commonly seen in females whose hair-grooming practices (eg, certain hairstyles, use of chemical relaxers combined with any pulling forces on the hair) result in excessive tension and trauma to the hair. *Trichotillomania*, or compulsive hair-pulling, may be seen at any age; however, onset is typically between the ages of 5 and 12 years (see Chapter 54). It affects females more often than males and children more than adults.

Pediatric discoid lupus erythematosus is rare, with a female predominance. Epidemiology data on the incidence of secondary

syphilis in the pediatric population are limited. Meanwhile, the prevalence of Menkes disease (kinky hair syndrome) is estimated to be about 1 in 100,000 live births. Among the causes of diffuse hair loss in children (ie, telogen effluvium, anagen effluvium, and loose anagen syndrome), telogen effluvium is the most common.

Clinical Presentation

Children may present with specific symptoms, including localized baldness, pruritus, scaling, or inflammation (Box 136.1). Occasionally, lymphadenopathy, particularly in the occipital area, is the major presenting symptom.

Pathophysiology

An understanding of the physiology of the typical hair growth cycle helps in the evaluation of hair and scalp disorders. The average human scalp contains approximately 100,000 hairs. Individuals with blonde hair generally have 10% more hairs; those with red hair have 10% fewer. Healthy terminal hair grows an average of 0.3 mm (0.01 in) per day, or 1 cm (0.4 in) per month. Typical hair growth is a cyclic process composed of 3 stages. The *anagen phase,* the period of active hair growth, lasts for an average of 3 years (range: 2–6 years). Normally, about 85% to 90% of scalp hair is in this phase at any 1 time. The *catagen phase,* the transition period, lasts for about 10 to 14 days. The *telogen phase,* the final resting phase, lasts for about 3 to 4 months. About 13% of scalp hairs are in this phase at 1 time. The average individual loses about 100 to 150 telogen hairs per day. The typical hair cycle results in replacement of each scalp hair every 3 to 5 years.

Scalp Disorders Without Associated Hair Loss

Among the scalp disorders affecting newborns that are not associated with hair loss, both caput succedaneum and cephalohematoma are caused by birth trauma. Meanwhile, scalp abscess and herpesvirus are neonatal infections caused by rectovaginal bacterial flora and herpes simplex virus, respectively. The pathophysiology for atopic and seborrheic dermatitis is described in detail in Chapter 138. Head lice and scabies are infestations caused by *Pediculus humanus capitis* and *Sarcoptes scabiei*, respectively.

Box 136.1. Diagnosis of Disorders of the Hair and Scalp in Pediatric Patients

- Circumscribed or generalized hair loss (alopecia)
- Scaling
- Pruritus
- Erythema of the scalp
- Localized or generalized swelling of the scalp
- Occipital adenopathy

Scalp Disorders Associated With Hair Loss

Nevus sebaceus, a congenital scalp disorder that presents as a hairless plaque, is thought to be caused by noninherited mutations associated with a defect in the ectoderm, consequently resulting in hyperplasia of the epidermis and sebaceous glands. Aplasia cutis congenita occurs sporadically; however, familial cases have been reported. Aplasia cutis congenita is thought to be a result of many possible etiologies, including exposure to teratogens and trauma, and it can be an isolated defect or occur in association with other congenital defects such as cleft lip or palate, syndactyly, or multiple other genetic anomalies.

Tinea capitis is a communicable fungal infection and can be acquired via interpersonal contact, contact with infected animals, and fomites. There are 3 patterns of hair invasion. In endothrix infections (eg, *T tonsurans*), the fungus produces chains of spores within the hair shaft. In ectothrix infections (eg, *M canis*), spores are present around the exterior of the hair shaft. Favus, the most severe form of tinea capitis, demonstrates hyphae and air spaces within the hair shaft. This is usually caused by *Trichophyton schoenleinii,* a less common etiologic organism. Although dermatophytes have a relatively short incubation period (up to 3 weeks), they are viable in fomites for months. On close examination with dermoscopy, hairs may have a comma or zigzag appearance, with endothrix and ectothrix infections, respectively. Subcutaneous invasion in conjunction with an exaggerated host response can result in kerion, a boggy swelling of the scalp. Kerions are more commonly caused by a zoophilic dermatophyte, namely, *M canis.*

Pathophysiologic mechanisms of alopecia areata are not clearly known. One possible contributing factor is the aberrant expression of class 1 human leukocyte antigens on early anagen follicles, resulting in T lymphocyte recognition of these hairs, which are normally not recognized as foreign. There follows an immunologic attack causing premature transition to the telogen stage. The hairs then break easily at the surface of the scalp.

Traction alopecia and trichotillomania are caused by trauma to the hair. Discoid lupus erythematosus is an autoimmune condition thought to be multifactorial in etiology; the interplay of factors including genetic predisposition, sun exposure, and environmental toxins may lead to development of this condition. Secondary syphilis is caused by the bacterium *Treponema pallidum,* which can be transmitted during pregnancy through transplacental transmission, or through sexual contact. *Treponema pallidum* is not transmitted through human milk. Menkes disease is a congenital genetic disorder affecting copper uptake from the intestine, consequently resulting in copper deficiency. It is characterized by sparse kinky hair, failure to thrive, and neurodevelopmental deterioration. Telogen and anagen effluvium are 2 types of temporary hair shedding that occur at different growth stages of the hair cycle.

Differential Diagnosis

While some hair and scalp disorders can be easily recognized clinically, the differential diagnosis can be challenging at times.

Scalp Disorders Without Associated Hair Loss

These conditions are divided into those disorders seen most often in neonates and young infants and those seen more frequently in children and adolescents (Box 136.2).

Caput succedaneum, a generalized edema involving the soft tissues of the scalp, and cephalohematoma, a subperiosteal hematoma, are 2 of the most common lesions of the scalp that occur during the neonatal period, often caused by birth trauma. A cephalohematoma does not extend beyond the suture lines of the affected bone, which distinguishes it from caput succedaneum.

Other neonatal scalp conditions include infections such as scalp abscess and human herpesvirus infection. Scalp abscess occurs most commonly as a complication of scalp electrode placement. The infectious agents are usually flora of the cervix and vagina. Although most cases are self-limited, the abscess can be complicated by intracranial infection and/or sepsis. Patients who appear ill or have unstable vital signs may warrant additional workup, including blood cultures and/or neuroimaging based on clinical impression. Human herpesvirus infections of the scalp are not uncommon in neonates. Herpes lesions are typically vesicular, but petechial, purpuric, or bullous lesions may also be apparent. Skin lesions typically develop at 1 week after birth but may be present at birth or develop as late as 3 weeks later.

Seborrheic dermatitis and atopic dermatitis are the 2 most common diagnoses of scalp scaling among infants and children younger than 10 years. *Seborrheic dermatitis* is a red, scaly eruption that occurs mainly on the scalp (also known as cradle cap), face, and postauricular and intertriginous areas (see Chapter 138). It is often seen in infants and children younger than 2 years. Additionally, the scale, often termed *dandruff* in children 2 to 10 years of age, is usually associated with seborrheic dermatitis, and this is seen more in black children. Unlike atopic dermatitis, seborrheic dermatitis is generally non-pruritic. Occasionally, the inflammatory process is severe enough to result in diffuse hair loss. Psoriasis and Langerhans cell histiocytosis presenting on the scalp can mimic seborrheic dermatitis. Skin biopsy may be required for definitive diagnosis. Seborrheic dermatitis is often seen in conjunction with adenopathy of the head and neck without associated tinea infection.

Atopic dermatitis on the scalp is also characterized by erythema and scaling of the scalp, and it can overlap with seborrheic dermatitis. Atopic dermatitis on the scalp can be associated with significant pruritus with rubbing and scratching that result in the secondary effects of crusting and lichenification. Severe atopic and seborrheic dermatitis, as well as psoriasis, can result in pityriasis amiantacea (also known as tinea amiantacea, although it is not a fungal infection). *Pityriasis amiantacea* is a scalp condition that usually presents as localized, thick, adherent, and white or gray scale.

Head lice (pediculosis capitis) is an extremely common childhood infestation that affects girls more often than boys and is most common in children aged 3 to 11 years. Lice are spread by direct contact with infected individuals or infested clothing, combs, or other hair accessories. Pruritus is the primary symptom along with erythema and scaling, with secondary impetigo being common. The viable ova or nits may be visible as small, oval, tan to brown specks found most commonly attached to the hair above the ears and the nape of the neck. Hatched eggs are clear to white. Generally, only the ova closest to the scalp are viable. They are difficult to remove. Scabies, a pruritic infestation commonly seen in children, generally does not affect the scalp, except in infants, the elderly, and those who are immunocompromised. On the scalp of infants, 2- to 3-mm (0.08- to 0.1-in) erythematous papules are seen, with overlying excoriations and, often, secondary bacterial infection.

Box 136.2. Common Disorders of the Scalp Without Associated Hair Loss

Neonatal Period and Early Infancy

- Birth trauma to the scalp (eg, caput succedaneum, cephalohematoma)
- Scalp abscess (at fetal scalp electrode site)
- Herpes simplex infection
- Cradle cap/seborrheic dermatitis
- Atopic dermatitis[a]
- Scabies

Childhood and Adolescence

- Seborrheic dermatitis[a]
- Atopic dermatitis[a]
- Head lice (pediculosis capitis)
- Psoriasis[a]

[a] May occur with or without associated hair loss.

Scalp Disorders Associated With Hair Loss

Box 136.3 lists the common scalp disorders associated with hair loss. When evaluating hair loss in children, it is important to determine whether the loss is diffuse or circumscribed.

Nevus sebaceus is a benign, congenital growth characteristically presenting on the face or scalp. These lesions are characteristically hairless. In addition, they are usually solitary, well-circumscribed plaques on the scalp, yellow-orange in color, and ovoid to linear in shape. Nevus sebaceus can be associated with a small risk of malignant transformation, namely basal cell carcinoma, at a rate of less than 1% before the age of 18 years. Other benign growths within nevus sebaceus may also occur at a rate of approximately 1%. Therefore, regular monitoring or consideration of excision should be part of the management. Because of the relatively low risk and low metastatic potential, it is reasonable to postpone excision until later in life. Aplasia cutis congenita is a congenital skin defect with localized areas of epidermal, dermal, or subcutaneous tissue loss. Lesions can occur anywhere on the body, but most are found along the midline of the scalp. At birth, the lesions usually appear as punched out, round or oval defects that may have an overlying thin, glistening membrane. Erosion, ulceration, or a scar due to healing in utero can also be seen. A hair collar sign, or ring of long and coarse hair, may surround the lesion.

Box 136.3. Common Disorders of the Scalp With Associated Hair Loss

Circumscribed Hair Loss

Congenital

- Aplasia cutis congenita
- Nevus sebaceus
- Epidermal nevus

Acquired

- Tinea capitis
- Alopecia areata
- Traction alopecia
- Trichotillomania
- Discoid lupus erythematosus
- Secondary syphilis
- Human herpesvirus
- Lichen planus

Diffuse Alopecia

Congenital

- Congenital hypothyroidism
- Hair shaft defects (eg, Menkes syndrome, monilethrix)
- Ectodermal dysplasia and other genetic syndromes

Acquired

- Seborrheic dermatitis
- Psoriasis
- Telogen effluvium
- Anagen effluvium (secondary to toxins or chemicals)
- Endocrine (eg, diabetes mellitus)
- Hypothyroidism-hypoparathyroidism-hypopituitarism
- Medication-induced (isotretinoin)
- Androgenic alopecia (eg, male pattern baldness)
- Loose anagen syndrome

Other

- Nutritional (eg, acrodermatitis enteropathica, malnutrition, iron deficiency, rickets)
- Systemic lupus erythematosus

Tinea capitis, a fungal infection of the scalp, is among the most common causes of acquired hair loss in children. This condition is characterized by patchy alopecia with broken-off hairs and scaling of the scalp and may lead to scarring if the infection becomes inflammatory. *Trichophyton tonsurans* currently accounts for most cases in the United States, but in a given geographic area, the etiologic fungus may change over time. *Trichophyton tonsurans* infection sometimes appears as a series of black dots within the affected area because of the presence of fragmented hairs. Human-to-human transmission is more common with *T tonsurans,* an anthropophilic fungus. Children who handle dogs or cats, which harbor *M canis,* a zoophilic fungus, are susceptible to infection. Carriers are most commonly adults exposed to affected children, and carriers are potentially contagious and warrant screening and consideration of treatment. The diagnosis of tinea capitis can be difficult in children with diffuse scalp scaling or a diffuse pustular eruption without significant alopecia. Patients with tinea capitis may have palpable cervical lymphadenopathy on examination. Occasionally, an intense hypersensitivity response may result in a boggy swelling of the scalp known as a kerion. The surface of the kerion may be smooth or covered with small pustules, mimicking a bacterial infection. Tinea capitis lesions can present with scale and localized patches of hair loss and may lead to scarring if the infection becomes inflammatory. Uncomplicated tinea capitis leaves no scars, but kerion or favus may result in permanent, scarring hair loss.

Alopecia areata, which frequently leads to hair loss, is characterized by well-defined areas of complete hair loss without associated scaling, irritation, or inflammation of the scalp. The hairs at the margins of alopecia are easily plucked and have an "exclamation mark" appearance with the proximal end thinner than the distal end. The most common presentation is that of 1 or more round or oval bald patches. A less common subtype is the ophiasis pattern, in which hair loss is present in a band along the periphery of the temporal and occipital scalp. With alopecia areata, spontaneous regrowth with nonpigmented, white or gray hairs may initially be seen. However, patients may develop a new bald patch at another site despite regrowth at the initial location. Associated nail defects, including nail pitting (most common) and ridging, may occur. Occasionally, alopecia totalis (loss of all scalp hair) or alopecia universalis (loss of all body and scalp hair) may result. It may be seen in association with atopic dermatitis, Down syndrome, and other autoimmune diseases (eg, thyroid disease, vitiligo, inflammatory bowel disease). Family history is positive in 10% to 50% of affected patients.

Common traumatic causes of alopecia in children are traction alopecia and trichotillomania. Traction alopecia often occurs along the margins of the hairline secondary to having the hair pulled back in tight ponytails or braids. Short, broken hairs with patchy hair loss and follicular papules may be seen. Chronic, prolonged traction can result in permanent, scarring alopecia. Obtaining a history of hair care habits, including use of styling tools, headgear, and chemicals (eg, relaxants, dyes), is crucial. Trichotillomania is a self-induced form of traction alopecia in which children twist or pull out their hair either consciously or subconsciously and may be seen in association with other impulse disorders such as thumb-sucking and nail-biting (see Chapter 54). It results in hair loss caused by self-induced trauma. Usually scalp hair is involved, but any hair-bearing areas, including eyebrows or eyelashes, may also be affected. Hairpulling is generally believed to occur in a younger population and usually resolves with minimal or no intervention needed. Trichotillomania is classified in *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition, in the Habit and Impulse Disorders category. Hair is generally plucked in a wavelike fashion across the scalp or centrifugally from a starting point. The occiput is generally spared. Trichotillomania may mimic other types of alopecia, but the diagnosis can usually be made on the basis of the bizarre patterns of hair loss with hairs broken at differing lengths. Children occasionally eat the hairs as they are pulled out, resulting in the formation of a trichobezoar (hair ball) in the stomach.

Discoid lupus erythematosus, lichen planus, and secondary syphilis are uncommon causes of localized hair loss from the scalp in children. The patches of alopecia in discoid lupus erythematosus often appear hypopigmented with hyperpigmentation at the periphery, the latter representing older lesions. Because adnexal structures are involved in discoid lupus, scarring alopecia is commonly seen. Lichen planus, an idiopathic inflammatory disease of skin and mucous membranes, can result in scarring and non-scarring alopecia. Secondary syphilis lesions appear as diffuse, "moth-eaten" patches of alopecia often affecting the occipital or bitemporal scalp regions that are non-scarring. In addition to the scalp, other areas, including the eyebrows, eyelashes, and body hair, may also be affected.

A variety of structural defects, endocrine and metabolic disorders, and toxins may be associated with diffuse loss of scalp hair (Box 136.3). Intrinsic structural defects of the hair may cause hairs to break, thus resulting in failure of hair growth. In some forms of ectodermal dysplasia, the number of hair follicles is reduced or the follicles are altogether absent, giving the appearance of sparse or thinning hair. Many of the ectodermal dysplasias have abnormalities of the teeth, nails, and sweat glands. Monilethrix is an autosomal-dominant condition that can appear in isolation or in association with other anomalies. Microscopic evaluation of hairs shows a "beads on a string" appearance due to alternating nodes and internodes resulting in fractures between the nodes. Pili torti can be seen in several syndromes, including Menkes disease (kinky hair syndrome). Affected patients have twisted hair leading to premature breakage and, thus, chronically short hair. There is often baldness at sites of friction.

Causes of diffuse hair loss in childhood include telogen effluvium, anagen effluvium, and loose anagen syndrome. Telogen effluvium is a common cause of diffuse, non-scarring hair loss that may occur 2 to 4 months after a variety of events, including pregnancy, discontinuation of oral contraceptives, severe febrile illness, medications, severe diets, or significant emotional stress. Hair loss results from the abrupt conversion of numerous scalp hairs from the anagen (growth) phase to the telogen (resting) phase. Loss of more than 150 hairs per day is considered atypical. Patients may report losing several hundred hairs a day, but the occurrence of clinically significant baldness is rare. Estimates indicate that individuals must lose about 25% of their hair before thinning becomes clinically apparent. The hair loss may continue for several weeks, but complete regrowth usually occurs within 6 to 12 months, or after reversal of the inciting trigger. *Anagen effluvium* results in the loss of growing hairs due to a sudden cessation of the growing phase. It occurs most commonly after systemic chemotherapy but can also occur with exposure to radiation or toxins. *Loose anagen syndrome* is a disorder in which the anagen hair follicle is anchored improperly, resulting in easy, painless plucking of the hairs. This can result in patchy diffuse hair loss or focal areas of alopecia without increased hair fragility. This is a familial condition, with fair-haired females more commonly affected. Often, these children will not need a haircut through early childhood. The hair is expected to spontaneously become normal by the teenage years without treatment. Thyroid disorders, particularly hypothyroidism, can also result in diffuse congenital or acquired hair loss.

Evaluation

History

The age of the child guides the differential diagnosis because some lesions are more common at one age than another. Box 136.4 reviews pertinent history that may be helpful in diagnosis.

Physical Examination

The scalp should be examined to see if hair loss is diffuse or circumscribed and whether scalp hairs can be plucked easily. Signs of irritation, inflammation, or scaling of the scalp should also be noted, as well as the presence of adenopathy, nail changes, or hair loss elsewhere on the body.

Wood light examination of the scalp for fungus is helpful if the result is positive. A negative examination does not rule out the possibility of fungal infection, however, because *T tonsurans,* the most common cause of tinea capitis in the United States, does not fluoresce. *Microsporum canis* fluoresces yellow-green under the Wood light.

Laboratory Tests

Laboratory assessment is useful in some cases. If fungal infection is suspected, a potassium hydroxide examination should be performed by the primary care physician. Scales and broken hairs can be obtained from involved areas by brushing, scraping (eg, with a No. 15 scalpel blade), plucking, or rubbing a moistened 10- × 10-cm (3.9- × 3.9-in) gauze over affected areas and then removing broken hairs and scale from the gauze with forceps. The scrapings should be placed on a glass slide, dissolved in potassium hydroxide solution, heated gently, and examined under the microscope. Hyphae and spores within the hair shaft (eg, *T tonsurans* infection) or surrounding the hair shaft (eg, *M canis* infection) should be noted.

Box 136.4. What to Ask

Disorders of the Hair and Scalp

- Is the child losing any hair?
- If so, is the child losing hair from all over the scalp or only from localized areas on the scalp?
- Has the child lost any body hair (eg, eyebrows, eyelashes) in addition to the scalp hair?
- How long has the child been losing hair?
- Is the scalp pruritic or scaling?
- Have the parents noticed the child twisting or pulling the hair?
- Is the child's hair often in ponytails or braids?
- Has there recently been any significant stress in the child's life?
- Do any pets live in the home?
- Is the child taking any medications?
- Is anyone else in the home or anyone in close contact with the child having similar symptoms?

In addition to microscopic examination, fungal cultures are recommended in all cases of suspected tinea capitis. Brushings using a moistened sterile cotton swab or a sterile brush as used in Papanicolaou tests will yield the most reliable results. Hair or scalp scrapings are inoculated onto Sabouraud agar or dermatophyte test medium. Within 5 to 14 days, a distinctive growth seen on the Sabouraud agar or a color change from yellow to red in the dermatophyte test medium confirms the diagnosis. Negative potassium hydroxide examination and fungal culture results, in addition to a lack of inflammation and scaling, may be required for differentiating trichotillomania or alopecia areata from tinea capitis.

The diagnosis of telogen effluvium is usually suggested by the history and counting the number of hairs lost each day. If the diagnosis is in question, the patient may be referred to a dermatologist for examination of the involved hair roots via biopsy and determination of the anagen to telogen ratio, which is usually about 85:15. A telogen count of more than 25% is considered to be diagnostic of telogen effluvium. The ratio of anagen to telogen hairs is normal in trichotillomania. For cases in which the trigger for suspected telogen effluvium is unknown, additional laboratory workup (ie, chemistry panel, thyroid function tests, hematocrit, ferritin, and sedimentation rate) should be performed. In persistent cases, a scalp biopsy may be obtained.

A more extensive laboratory workup may be required if the hair loss is persistent or the history or physical examination is suggestive of systemic disease (Box 136.3). Studies that may be considered include liver function tests, thyroid function studies, a serum VDRL test, antinuclear antibodies, and serum electrolytes. Routine thyroid function studies should be reserved for patients with alopecia areata with a personal history of atopy or Down syndrome, family history of thyroid disease, or clinical findings suggestive of thyroid disease. Low vitamin D has been linked with alopecia areata, with one study finding deficient levels of 25(OH) vitamin D in the serum of patients with alopecia areata, and an inverse relationship between serum vitamin D and disease severity.

Management

Scalp Disorders Without Associated Hair Loss

Management depends on the diagnosis. Cephalohematoma and caput succedaneum result from birth trauma and generally resolve spontaneously within a few weeks to months without further complications. Meanwhile, management of scalp abscesses includes incision and drainage alone for uncomplicated cases and consideration of systemic antibiotics depending on the severity of the infection (eg, associated cellulitis, signs of systemic involvement). Herpetic infection in a newborn requires immediate attention and systemic antiviral therapy because the risk of systemic infection is significant. Scalp electrodes and vacuum-assisted vaginal deliveries should be avoided in neonates with mothers known to have human herpesvirus infections because these can increase the rate of infection transmission. Currently, cesarean section remains the standard of care, although most cases of herpes simplex in neonates are in those born to mothers without known infection at time of delivery.

Seborrheic dermatitis can persist into the pubertal years, contrary to previously held beliefs. Cradle cap, which refers to seborrheic dermatitis seen during infancy, can be treated with simple skin care measures such as bathing and the use of moisturizing emollients. Gentle shampoos, low-potency corticosteroids, and, if needed, 2% ketoconazole cream can resolve most cases. Past infancy, seborrheic dermatitis may be treated with shampoos containing tar, zinc pyrithione, ketoconazole, or selenium in rotation. Topical, mild corticosteroid solutions can be used if pruritus is significant. As with the management of atopic dermatitis elsewhere in the body, the goals of treatment for atopic dermatitis involving the scalp include reducing environmental triggers and minimizing inflammation and pruritus of the skin. Treatment modalities typically include topical corticosteroids, topical calcineurin inhibitors, and phototherapy (see Chapter 138).

Head lice may be treated with pyrethrin products, such as permethrin 1% cream rinse (Nix) or the prescription 5% cream typically used for scabies. Other medications can also be effective. Topical ivermectin (Sklice Lotion) was approved by the US Food and Drug Administration in 2012 for use in patients 6 months and older with head lice. Topical malathion (Ovide Lotion) is another option, although it is flammable given its high concentration of isopropyl alcohol. Lindane shampoo may be considered in patients who have head lice refractory to treatment. Of note, lindane shampoo has a US Food and Drug Administration black box warning given the possible risks of neurologic toxicity. All topical medications should be used twice, 1 week apart, regardless of package insert information. A fine-toothed comb or tweezers may be required after rinsing to remove the ova or nits of head lice. Other alternative treatments have been unsubstantiated, such as using mayonnaise or petroleum jelly. Heat, such as that associated with blow-drying the hair, also kills a large percentage of the lice. The timing of when children infested with head lice can return to school is controversial. Some school authorities recommend a no-nit policy that prohibits children with nits from returning to school, even if the nits are not viable. Groups including the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics do not support adherence to the no-nit policy once children are treated. Per the CDC, many of the nits are 0.6 cm (0.25 in) or more from the scalp and typically not viable. In addition, the disadvantages of unnecessary absences from school outweigh the low probability of transmission.

For treatment of scabies, permethrin 5% cream is the preferred scabicide. It should be applied from head to toe in infants and children younger than 2 years and from neck to toe for those older than 2 years, for 8 to 12 hours, washed off, and repeated in 1 week. Permethrin 5% cream can be used in infants as young as 2 months and pregnant women. For these patients, sulfur 6% ointment can also be used. For scabies and lice, the treatment of fomites is also important. Clothing, bed linens, and towels should be washed in hot water

and machine-dried in high heat. Fomites that cannot be laundered should be sealed in plastic for 48 to 72 hours.

Scalp Disorders Associated With Hair Loss

Children suspected of nevus sebaceus should be referred to a dermatologist. Excision may be considered not only because of the risk, albeit low, of secondary neoplastic changes but also because these lesions can become more prominent and warty in appearance and friable during puberty and adulthood. In cases of aplasia cutis congenita, small defects generally heal well with conservative management, whereas larger defects may require surgical excision and eventual skin grafting. Preoperative imaging studies may be required for extensive, severe cases.

Both oral griseofulvin and terbinafine hydrochloride are effective treatment options for children with tinea capitis. Terbinafine appears to be more effective for individuals with *T tonsurans* infection, while griseofulvin is preferred for those with *M canis* infection. Oral griseofulvin administered for at least 6 to 12 weeks has been the long-held treatment of choice for tinea capitis. Although griseofulvin can have many side effects, including gastrointestinal disturbances, hepatotoxicity, and leukopenia, it is generally well tolerated by children and is available in suspension form. Care should be taken to use proper dosing when using micronized (20–25 mg/kg) or ultra-micronized (10–15 mg/kg) griseofulvin. Terbinafine, available in tablets or granules, has been effective at shorter treatment times than griseofulvin. Newer antifungal agents are also being used with great success, often for shorter durations than griseofulvin, which can increase compliance. Itraconazole and fluconazole are alternative treatments, specifically for those infected with *Trichophyton* species. Itraconazole can be given as continuous or pulse therapy and is available as a solution. Fluconazole, also available as solution, is usually administered for 3 to 6 weeks or at a higher dose once weekly for 8 to 12 weeks. Ketoconazole is contraindicated because of its potential for adverse effects, including liver toxicity and adrenal insufficiency, especially in light of other available agents. Generally, longer courses of treatment are needed for *M canis* infection. Topical antifungal agents are not effective on the scalp for treatment of tinea capitis because the hair follicle must be penetrated, requiring the use of systemic therapy. Twice-a-week shampooing with ketoconazole or selenium sulfide shampoos has been shown to reduce carriage of spores and reduce infectivity.

A course of oral prednisone may be required in conjunction with an oral antifungal if a kerion is present to minimize discomfort and permanent, scarring hair loss. Children with kerion are often misdiagnosed as having a bacterial infection of the scalp and treated with oral antibiotics. However, the pustules in kerion are generally sterile, and even when secondary bacterial infection is present (ie, about 30%–50% of patients), antibiotics do not alter the course of the condition.

Children believed to have alopecia areata should be referred to a dermatologist. Therapy for alopecia areata consists of topical and intralesional corticosteroids, topical anthralin, or minoxidil. Topical immunotherapy with a sensitizer such as squaric acid has also been used for the treatment of extensive alopecia areata. Occasionally, oral steroids can be tried for extensive or rapidly progressing disease. Tofacitinib, a Janus kinase inhibitor, has recently been proposed as a well-tolerated therapy for patients with alopecia areata, including adolescents. Many psychosocial factors should be considered when treating children with this condition. Children with severe forms of the disease may benefit psychologically from wearing a wig. The National Alopecia Areata Foundation (www.naaf.org) is available as a support group for affected children and their families.

Prevention and management of traction alopecia includes modifying hairstyling practices to minimize tension on the hair and scalp. No treatment has been demonstrated to be consistently effective for children with trichotillomania, although cognitive behavioral therapy and the use of antidepressants, including clomipramine hydrochloride, have been reported to have some success. Cessation of the inciting triggers of telogen and anagen effluvium (eg, drugs, toxins, stress) should lead to regrowth of hair.

Diligent sun protection is crucial in the management of discoid lupus erythematosus. Topical medications are the first-line therapy, with corticosteroids preferred over calcineurin inhibitors. Menkes disease has no cure. Given that it is a copper deficiency condition, some individuals with this disease may achieve benefits with copper injections. Children with Menkes disease often benefit from a multidisciplinary team, including physical and occupational therapists, nutritionists, gastroenterologists, and urologists, given the systemic nature of this condition.

The recommended regimen for infants and children with secondary syphilis is a single dose of intramuscular benzathine penicillin G (50,000 units/kg, up to adult dose of 2.4 million units). The CDC advises that all infants (>1 month of age) and children diagnosed with syphilis should be evaluated by a pediatric infectious disease specialist and evaluated for sexual abuse. Additionally, individuals diagnosed with syphilis should also be tested for HIV.

Prognosis

Common disorders of the scalp, such as seborrheic dermatitis, head lice, and tinea capitis, generally respond well to treatment and rarely result in long-term sequelae. The course and prognosis of alopecia areata are quite variable and may be difficult to predict. Generally, prognosis for regrowth is good if hair loss has occurred in only a few patches. Prognosis is usually poorer with younger age at onset, positive family history, nail involvement, and an ophiasis (band-like) pattern of hair loss. It is important to pursue further workup if a condition does not respond to therapy because it is critical that a condition such as Langerhans cell histiocytosis, which mimics seborrheic dermatitis, not be missed. Many of the hair disorders are a result of syndromes that will not respond to therapy; thus, education for patients and their families is important.

CASE RESOLUTION

The child exhibits physical findings of a kerion. Diagnosis can be made clinically on the basis of the appearance of the lesion. The diagnosis is established by microscopic evidence of hyphae and culture confirmation. Treatment with oral antifungals and possibly oral steroids should be initiated. Carriers should also be identified and treated. The child should be examined in 4 weeks to ascertain the response to therapy and check for any adverse reactions.

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CHAPTER 137

Diaper Dermatitis

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CASE STUDY

A 6-month-old boy has a 3-day history of a rash in the diaper area. The mother has been applying cornstarch, but the rash has worsened and spread to the inner thighs and abdomen. The infant has no history of fever, upper respiratory tract symptoms, vomiting, or diarrhea. He was seen in the emergency department 1 week prior to this office visit for acute gastroenteritis, which has since resolved. On examination, a poorly demarcated, shiny, erythematous rash is noted over the convex surface of the buttocks, lower abdomen, and genitalia, with relative sparing of the intertriginous folds. The rest of the physical examination is within normal limits.

Questions

1. What are the common causes of rashes in the diaper area (ie, diaper dermatitis)?
2. What features distinguish the various types of diaper dermatitis?
3. What systemic diseases may present with diaper dermatitis?
4. What are complications that may affect dermatitis in the diaper area?
5. What are some common treatments for diaper dermatitis?

Diaper dermatitis (DD) is a nonspecific term used to describe the various inflammatory reactions of the skin within the diaper area. Diapered skin is exposed to friction, excessive hydration, and varying pH; additionally, it is in constant contact with urine and stool, both of which are highly irritating to the skin. Management of DD focuses on acceleration of healing of the damaged skin and prevention of a recurring rash. More importantly, the key to efficient DD management is prevention.

Epidemiology

Diaper dermatitis is the most common dermatologic disorder in infancy, with a peak incidence at 9 to 12 months of age, although some reports have shown a high incidence in the first month after birth. The prevalence of reported DD in infants varies greatly, from 7% to 50%. This disorder is not limited to infants and small children; it may occur in any individual who wears diapers, although the prevalence in adults is unknown.

Clinical Presentation

Diaper dermatitis primarily affects the skin of the buttocks, gluteal cleft, lower abdomen, genitalia, perineum, and proximal thighs. The 3 most common types of DD are chafing dermatitis, irritant contact dermatitis, and diaper candidiasis. The different types of DD have distinct clinical presentations. *Chafing dermatitis* is quite common in infants and appears in areas in which friction from the diaper is most severe. It appears as mild redness in the affected area and improves quickly on its own with frequent diaper changes and/or decreased friction. The most common type of DD, *irritant contact dermatitis*, appears as scaly erythematous papules and plaques or poorly demarcated, glistening erythema over the convex surfaces, with relative sparing of the intertriginous folds (Figure 137.1A). *Diaper candidiasis* is another common form of DD and presents as well-defined red plaques with satellite papules and superficial pustules along the margin. Candidal infections may be primarily concentrated within the skin folds (Box 137.1) (Figure 137.1B).

Pathophysiology

The development of all 3 main subtypes of DD is the result of multifactorial interaction, of which the most important is prolonged contact of the skin with urine and stool. Other factors characteristic of the diaper area are excessive moisture, elevated pH, high enzymatic activity, and friction, all of which to some extent compromise the skin barrier function and induce a skin inflammatory reaction.

Prolonged wetness in the diaper area results in maceration of the stratum corneum. Weakening of its physical integrity makes the stratum corneum more susceptible to mechanical friction generated as the diapered infant tries to move, local irritation resulting from chemicals or enzymes, and microbial infections. Urine and stool can elevate the local pH to more alkaline values and in turn cause increased activity of fecal proteases, lipases, and ureases, all of which are highly irritating to the skin. Furthermore, fecal ureases produced by a variety of fecal bacteria catalyze the breakdown of urea to ammonia, which in turn contributes to increased skin pH level. Friction generated as the infant tries to move about may further aggravate the condition and result in maceration of the skin. A damaged skin barrier can also result in microbial imbalance on the skin surface. *Candida albicans* and *Staphylococcus aureus* are typically isolated from the affected area and may further aggravate skin inflammation.

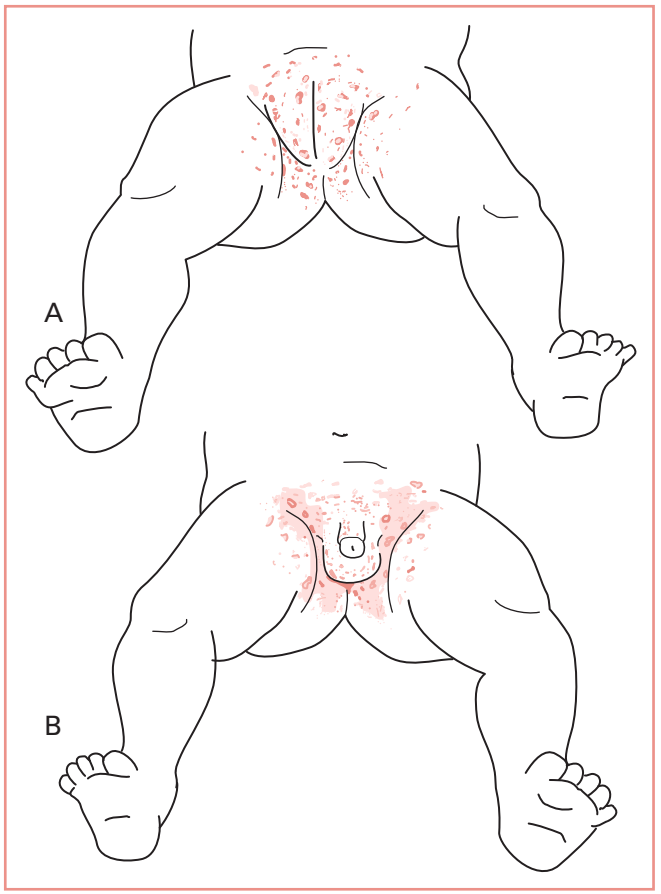

Figure 137.1. Diaper dermatitis. A, Diaper dermatitis secondary to irritant contact. Convex surface areas are affected. B, Diaper dermatitis secondary to *Candida*. Intertriginous areas are affected, and satellite lesions are present.

Box 137.1. Differential Diagnosis of Diaper Dermatitis

Most Common Causes

- Irritant contact dermatitis
- Candidiasis
- Seborrheic dermatitis

Less Common Causes

- Allergic contact dermatitis
- Impetigo
- Perianal streptococcal or staphylococcal disease
- Atopic dermatitis
- Psoriasis
- Zinc deficiency, including acrodermatitis enteropathica
- Biotin deficiency
- Langerhans cell histiocytosis
- Congenital syphilis

Differential Diagnosis

Although most cases of DD can be easily recognized clinically, it is important to consider other etiologies beyond the common types mentioned previously, especially when the condition is not responsive to therapy. Familiarity with the difference in appearance of these conditions is critical. The internet can be valuable by providing access to images of many dermatologic conditions. Some websites display a pictorial representation and allow for searching by features such as rash morphologies, symptoms, exposures, skin color, body location, and many other factors.

The differential diagnosis of DD is presented in Box 137.1.

Granuloma gluteale infantum is a possible complication of irritant DD that presents with violaceous nodules and plaques on the buttocks, vulva, scrotum, and perineum. Although these nodules and plaques are alarming in appearance, they are benign and will resolve after the dermatitis is cleared; scarring can occur, however. The development of granuloma gluteale infantum does not necessarily correlate with the severity of the preexisting irritant dermatitis. Jacquet erosive dermatitisis another potential complication in which the irritant dermatitis is severe. This form of dermatitis is characterized by small, well-demarcated erosions or ulcers that can also feature elevated borders. With chronic irritant dermatitis, a child may develop *perianal pseudoverrucous papules and nodules*, which are small bumps characterized by a flat-topped, moist, smooth, shiny surface. All 3 types—granuloma gluteale infantum, Jacquet erosive dermatitis, and perianal pseudoverrucous papules and nodules—are considered to be less common manifestations of irritant contact dermatitis.

Candidiasis, which is the result of infection with *C albicans,* typically begins in the folds (ie, intertriginous areas) and then spreads to other surfaces. Sometimes associated with oral thrush, candidiasis is also a common sequela of systemic antibiotic therapy. The rash appears as bright, beefy red plaques with sharp, raised borders and many small satellite papules, vesicles, and pustules along its margins, often with desquamation. *Candida albicans* can be a cause of secondary infection of already inflamed skin as well as a primary causative factor in some cases of DD. Recurrent diaper candidiasis can be associated with candidal colonization of the gut and oral cavity. Persistent diaper candidiasis in young children may be a sign of type 1 diabetes mellitus, chronic mucocutaneous candidiasis, or an underlying immune deficiency.

Seborrheic DD, like candidal DD, also primarily affects the intertriginous areas of the groin. The rash has a characteristic salmon-colored appearance with soft, yellowish scale. Satellite lesions can be seen. Seborrheic dermatitis of the face, scalp (including postauricular areas), neck, trunk, and proximal extremities usually is seen in association with seborrheic dermatitis of the diaper area.

Allergic contact dermatitis is a less common cause of DD but should be considered in patients who do not respond to standard therapeutic interventions. Possible allergens include the chemical makeup of the diaper itself or topical preparations such as soaps, emollients, and baby wipes that are applied to the diaper area. For example, rubber additives (eg, 2-mercaptobenzothiazole) found in the elastics of disposable diapers have been shown to cause allergic DD on the hips and outer buttocks. This distribution is reminiscent of a cowboy's gun holster, which has earned the condition the moniker "Lucky Luke" dermatitis. Methylchloroisothiazolinone, also known as methylisothiazolinone, is a combination preservative used in personal care and household products and is a common cause of

allergic contact dermatitis. Allergic contact dermatitis in the diaper area has been reported with increased frequency in babies on whom wet wipes containing methylisothiazolinone are used. Other allergens to consider are emulsifiers in topical preparations, fragrances, disperse dye, and preservatives.

Bacterial infections can exacerbate DD. Impetigo, especially bullous impetigo, is a not uncommon eruption in the diaper area. Bullous impetigo is caused by *S aureus* and is toxin mediated. The rash presents as vesicles that may enlarge into 3- to 5-cm (1.2- to 2-in) bullae that easily rupture, leaving superficial erosions with thick, honey-colored crusts. The associated systemic symptoms of fever and diarrhea may be present. Perianal bacterial disease can result from group A β-hemolytic streptococcus or *S aureus.* Classically, perianal streptococcal dermatitis manifests as well-demarcated, bright red, tender patches. Rectal bleeding and painful defecation may also be noted.

In 30% to 60% of infants born with congenital syphilis, the symptoms are the same as those of DD. Initially, there usually exists a bright erythematous morbilliform eruption that fades to a coppery color, often with scaling. Pustules can develop later. The buttocks, face, extremities, palms, and soles generally are affected.

Diaper rashes that persist despite seemingly adequate therapy should raise suspicion for other systemic diseases as the underlying cause. Though less common than irritant and seborrheic dermatitis and candidiasis, these conditions include psoriasis, atopic dermatitis, zinc deficiency, biotin deficiency, and Langerhans cell histiocytosis. Psoriasis may occur anywhere on the body, but lesions typically occur on the scalp, face, elbows, and knees. In infants, generally between 2 and 8 months of age, psoriasis may involve the diaper area. Lesions elsewhere on the body typically are well-circumscribed, erythematous plaques with a thick, silvery scale. Psoriatic lesions in the diaper area, however, may be difficult to differentiate from seborrheic dermatitis or candidal infection. Plaques are brightly erythematous and sharply demarcated but without obvious scale because of the moisture from the occluded diaper area. Skin biopsy, family history of psoriasis, or nail involvement may help confirm the diagnosis.

Atopic dermatitis typically spares the diaper area, even in infants who have lesions elsewhere on the body. The relative sparing of the diaper area may be a result of the increased moisture of the skin in this area. (See Chapter 138 for a discussion of atopic dermatitis.)

Zinc deficiency can cause dermatitis in a characteristic periorificial distribution (ie, mouth, nose, ears, eyes, and anogenital area) and in the distal extremities. Zinc deficiency may result from the inherited defect acrodermatitis enteropathica or may manifest secondary to insufficient intake or malabsorption, such as in patients with cystic fibrosis. *Acrodermatitis enteropathica* is a rare, autosomal recessive inherited disorder with mutations in *SLC39A* resulting in defective zinc transporters in the small intestine. In breastfed infants, the disease manifests shortly after weaning, whereas in bottle-fed infants, signs and symptoms appear days to weeks after birth. Afflicted infants are irritable and listless and present with diarrhea, failure to thrive, and skin lesions in the previously mentioned distribution, featuring erythematous bullous and pustular lesions as well as dry, red, scaly plaques. Candidal and *S aureus* superinfection can occur. Treatment consists of oral zinc supplementation. Biotin deficiency, as well as several other nutritional deficiencies, can present with identical skin findings, and treatment is with supplementation of the deficient nutrient.

Langerhans cell histiocytosis refers to a group of disorders characterized by proliferation of macrophages, a progenitor cell in the bone marrow. Members of this group include Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma, and congenital self-healing reticulohistiocytosis. Skin lesions may involve the scalp and flexural areas of the perineum, axilla, and neck. The lesions appear as small, pink to tan scaling papules and pustules that can coalesce; associated purpura or ulceration may be apparent in the inguinal fold with secondary impetiginization (ie, honey-colored crusting caused by *S aureus* superinfection). The rash is most often confused with seborrheic dermatitis. Diagnosis can be confirmed by skin biopsy.

Evaluation

History

A thorough review of the medical history is crucial for efficient diagnosis and management, including duration of the presenting rash, frequency of urination and defecation, other symptoms (eg, pain, itchiness), hygiene practices, and previously used therapies (Box 137.2). Diaper candidiasis should be suspected if oral antibiotic therapy has recently been administered.

Physical Examination

On physical examination, DD presents as an erythematous eruption with varying patterns as described previously. Based on the physical examination of the diaper area and presence of skin lesions elsewhere on the body, potential etiologies should be considered. This is particularly important in the case of a persistent, resistant, or recurrent diaper rash in which a generalized skin disorder, such as psoriasis, must be considered. The distribution of the rash within the diaper area itself may provide clues to the diagnosis. Candidiasis and seborrheic dermatitis occur primarily in the folds, whereas irritant contact dermatitis usually affects the convex areas of the skin with relative sparing of the intertriginous areas. Streptococcal disease manifests primarily as marked perianal erythema.

Box 137.2. What to Ask

Diaper Dermatitis

- When did the rash begin?
- Does the rash resolve and then recur?
- Is the rash pruritic?
- Is the infant feeding and sleeping? Is the infant irritable?
- Have any home remedies or previous treatments been used? If so, which ones?
- Does the infant have a family history of atopic dermatitis or psoriasis?
- Is the infant taking antibiotics now, or has the infant used them recently?
- What type diaper is used?
- How frequently are the diapers changed?

Laboratory Tests

Laboratory tests are rarely necessary in the evaluation of DD; however, they can be useful in confirming the etiology of atypical cases. Although the diagnosis of diaper candidiasis is usually evident clinically, microscopic examination of skin scrapings with potassium hydroxide may be performed to establish the diagnosis. Typically, budding yeast with hyphae or pseudohyphae is seen. The diagnosis of perianal streptococcal disease or bullous impetigo may be confirmed by bacterial cultures from the perianal area or bullous lesions, respectively. Biopsies may be warranted for the patient with recalcitrant DD. Other laboratory tests, such as viral culture, polymerase chain reaction, direct fluorescent antibody, or Tzanck, may be performed to exclude other suspected skin diseases.

Management

Management of DD is based on 2 major objectives: accelerating healing of the damaged skin and preventing recurrence. The key to efficient DD management, however, lies in prevention of the initial eruption.

Skin Care

The mainstay of DD prevention and management involves keeping the diaper area clean and dry. General skin care measures are needed for maintaining a healthy skin barrier. Gentle but thorough cleansing of the diaper area is necessary when stool is present and can be done with water alone or with water and mild cleanser. The area should then be patted dry and allowed to air-dry completely if possible; alternatively, cotton balls can be used to dry the area. Cleansing frequently with harsh soaps or scrubbing too vigorously can further irritate skin that is already damaged and inflamed.

Additionally, the diaper should be changed frequently. Cloth and standard disposable diapers are less effective than superabsorbent gel diapers in decreasing moisture. Dusting powders, such as cornstarch and talc, minimize friction. Unlike cornstarch, talc does not enhance the growth of yeast on skin. Concerns about the pulmonary effects from inhalation of cornstarch and talc precludes their routine use in the absence of any skin inflammation, however. Moisture-resistant barrier ointments or creams, such as zinc oxide and petrolatum, are quite helpful in reducing irritation. The role of hygiene in preventing and managing all forms of DD cannot be overemphasized. Topical application of medicated creams and ointments is not effective in the presence of poor hygiene.

Parent and caregiver education with clear explanation of DD etiology and general skin care measures in the diaper area are key to ensuring compliance and adherence.

Management of Diaper Dermatitis

In mild to moderate DD, the use of a topical barrier preparation as the first-line therapy is usually sufficient. More severe forms of DD with clinical signs of secondary infections require greater medical attention with careful diagnosis and therapeutic treatment.

Candidal infection is quite common in more severe cases of DD, and antifungal creams, such as nystatin, miconazole, ketoconazole, and sertaconazole, can be applied to the diaper area with every diaper change. Additionally, low-potency topical corticosteroids, such as 0.5% or 1% hydrocortisone ointment or cream may be required if inflammation is severe. Oral antifungal therapy is usually not indicated, although it may be necessary in cases of recurrent candidiasis.

If a secondary bacterial infection is present, topical or oral antibiotics may be necessary. If the bacterial infection is localized and mild, topical mupirocin applied twice a day for 5 to 7 days may be sufficient to treat a staphylococcal infection. Oral antibiotics (eg, cephalexin) may be required for more extensive bacterial infections, especially if the infant is febrile and/or ill-appearing.

A short duration of low-potency topical corticosteroid can reduce inflammation in DD that persists despite skin care measures and use of barrier preparations. Nothing stronger than 1% hydrocortisone should be considered. Additionally, as per the recommendation of most specialists, this should be applied only until the eruption has cleared and for no longer than 2 weeks. Combination topical medications containing a corticosteroid and an antifungal agent are not recommended routinely because they usually contain high-potency corticosteroids. When topical steroids and antifungal agents are used in conjunction with barrier ointment, the medication should be applied before the barrier ointment.

When the more common causes of DD, such as irritant contact dermatitis and *Candida,* do not respond to conventional therapy, further workup must be initiated because of the possibility for an underlying systemic disease manifesting as DD.

Prognosis

Although recurrence of DD is common, most patients respond well to topical medications and measures undertaken to keep the diaper area clean and dry.

CASE RESOLUTION

The infant has irritant contact dermatitis. He has a recent history of gastroenteritis, and stool is known to be particularly irritating to the skin. Treatment includes keeping the diaper area clean and dry with frequent diaper changes and use of superabsorbent diapers as well as topical application of a low-potency corticosteroid ointment or cream and a barrier ointment (eg, petroleum ointment).

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CHAPTER 138

Papulosquamous Eruptions

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CASE STUDY

A 6-month-old girl presents with an erythematous, confluent, slightly raised and scaly rash on the cheeks. The extremities are also covered with a fine papular rash. The infant has had some scaling behind the ears and on the scalp since early infancy, but the symptoms have recently increased. The mother has been applying baby oil to the scalp to relieve the scaliness. Except for some intermittent rhinorrhea, the infant has otherwise been well. Immunizations are deficient; she received only the first set when she was 2 months old. The family history is positive for bronchitis. The infant's weight is at the 75th percentile and height is at the 50th percentile. Vital signs are normal. The physical examination is normal except for the presence of the rash.

Questions

1. What are the characteristics of papulosquamous eruptions?
2. What are the common conditions associated with papulosquamous eruptions in children?
3. What are the appropriate treatments for common papulosquamous eruptions?
4. When should children with papulosquamous eruptions be referred to a dermatologist?

Rashes, a common problem in children, can be classified in ways that help to establish a diagnostic approach. First, rashes are assessed in terms of appearance: macular (flat), papular (raised), squamous (scaly), vesicular (fluid filled), or bullous (large, fluid filled). Next, the extent of the rash is determined. Rashes may be described as generalized or localized. Location is also important. The site of a localized rash may be consistent with certain diagnoses (eg, diaper dermatitis). Pruritus is an important distinguishing feature. Other systemic symptoms must also be taken into consideration. Rashes may be a primary skin condition or a manifestation of an underlying infection or reaction to a precipitating agent.

Papulosquamous eruptions are rashes characterized by scaly papules and plaques. Eczema is a broad group of skin disorders characterized clinically by scale and histologically by spongiosis and makes up a large component of the papulosquamous disorders. The etiology of many papulosquamous eruptions is unknown, and the clinical appearance of lesions is the reason they are classified together.

Epidemiology

Although a large number of conditions may cause papulosquamous eruptions in children, a select number of diagnoses account for most problems and are the focus of this chapter. One of the most common types of papulosquamous eruptions in children is atopic dermatitis. Atopic dermatitis has become increasingly more common, and the prevalence in school-age children in the United States is estimated to be between 10% and 20%. Positive family history is often elicited. The severity of atopic dermatitis generally improves with age; however, lifelong dry, itchy skin, in varying degrees of severity, is not uncommon. Seborrheic dermatitis is another common papulosquamous rash seen in the pediatric population. Although most commonly described in infants younger than 3 or 4 months, it can occur in all pediatric age groups. It is estimated to have a prevalence of up to 5%, encompassing pediatric and adult populations.

Scabies occurs worldwide and is frequently encountered in general pediatric and dermatologic settings. The prevalence is much greater in developing countries and in situations in which populations are forced into close proximity (eg, during wars, incarceration, in refugee camps). Scabies is transmitted through direct contact; thus, family members and close contacts are at greatest risk of infection.

Clinical Presentation

Papulosquamous eruptions consist of skin-colored to erythematous, scaly papules and plaques that may involve the face, trunk, or extremities. The lesions can be pruritic, and scratching may lead to crusting or secondary infection. Sometimes multiple family members are affected (Box 138.1). Chronicity and repeated manipulation may lead to lichenification (thickening) of involved skin.

Pathophysiology

The pathophysiology of atopic dermatitis has not been definitively established. Evidence suggests that mutations in the *FLG* gene, encoding a protein important for skin barrier function, may play a large role in atopic dermatitis. It is also important to keep in mind that atopic dermatitis is a multifactorial disease with variable expression, influenced by environmental factors. Inheritance of this disease

Box 138.1. Diagnosis of Papulosquamous Eruptions in Pediatric Patients

- Raised, scaly papules and plaques
- Pruritus
- Afebrile, unless secondary infection is present
- Personal or family history of allergies
- Intertriginous rash

is associated with atopy, made up of the triad of atopic dermatitis, allergic rhinitis, and asthma. The disorder is attributed largely to skin barrier function; however, immune dysfunction and reactivity of nerves and blood vessels may also be involved. Initially, the disease is characterized by Th1 cytokine predominance, but later in chronic disease, there is activation of the Th2 immune pathway with a resultant synthesis of cytokines, including interleukin (IL)-4 and IL-5, causing elevated immunoglobulin (Ig) E levels, eosinophilia, and diminished cell-mediated immunity. Elevated IgE is reported in up to 80% of patients with atopic dermatitis.

Like atopic dermatitis, the etiology of seborrheic dermatitis remains unclear. There may be an association with the yeast *Malassezia*, including the *Malassezia furfur* species (formerly known as *Pityrosporum ovale*), although whether this organism is causative is unclear. It is widely accepted that this yeast has some role in seborrheic dermatitis, which is further supported by the improvement observed with topical antifungal medications. Individuals with seborrheic dermatitis that is severe or extensive may have immune dysfunction, such as uncontrolled HIV/AIDS.

The inflammatory response in scabies is triggered by an infestation with the mite, *Sarcoptes scabiei.* The adult female burrows under the skin and lays 60 to 90 eggs. After 2 weeks, the eggs become adults. Affected individuals may be asymptomatic on first exposure. Up to 2 to 6 weeks after infestation, the host's immune system becomes sensitized to mites or scybala (mite feces), resulting in systemic pruritus and rash. In most individuals, the rash associated with scabies is an allergic phenomenon; each eruptive papule may not actually contain mites.

Differential Diagnosis

While many papulosquamous eruptions are clinically distinguishable, the differential diagnosis may be challenging at times. Familiarity with the appearance of these conditions and their differentiating features is critical.

Conditions that present as papulosquamous eruptions in children include atopic dermatitis and seborrheic dermatitis, as described previously; however, the differential diagnosis is vast and includes other conditions, such as contact dermatitis, psoriasis, pityriasis rosea, lichen planus, lichen striatus, scabies, and fungal infections of the skin.

Eczema is a general term used to describe a type of papulosquamous eruption. The most common eczematous conditions seen in children are atopic dermatitis, seborrheic dermatitis, and contact dermatitis. Atopic dermatitis is a disorder of infancy and childhood and may persist into adulthood. More than half of affected individuals are symptomatic by 1 year of age, and in 90% of cases onset occurs by 5 years of age. The area of involvement changes with age. In infancy, the face, scalp, and extensor surfaces are involved, often areas where the infant can relieve itching by rubbing, and the diaper area is often spared (Figure 138.1A). By childhood, the more typical pattern seen in adults becomes more common: involvement of flexural surfaces such as the neck and antecubital and popliteal fossae. Adults tend to have greater extremity involvement, along with the head and neck. The itching is typically worse at night and can be exacerbated by multiple triggers, including extreme temperatures, sweating, clothing with rough textures, and infections. Clinically, xeroderma (abnormally dry; also called xerosis), erythema, and a pruritic papular eruption are common. Scratching and rubbing lead to crusting and weeping. Eventually, the irritation and inflammation of the skin leads to thickening of the skin, known as *lichenification*. Changes in color, including hypopigmentation and hyperpigmentation, may also occur. *Pityriasis alba*, considered to be the mildest form of atopic dermatitis, presents as hypopigmented areas with fine scale, most commonly observed on the face. Xeroderma is a frequent coexisting condition. *Ichthyosis vulgaris*, characterized by dirty-appearing excessive scaling and hyperlinear palms, is present in up to one-half of patients affected with atopic dermatitis. Lesions around mucosa (Morgan folds in the infraorbital fold under the eye and cheilitis around the mouth) may also be seen. Symptoms of other atopic conditions, such as allergic rhinitis, asthma, or food-related allergies, may also affect these patients.

Seborrheic dermatitis, which frequently develops during the first 3 months after birth, is characterized by scaly papules or confluent waxy, scaly plaques, particularly of the scalp. Scalp eruptions in infancy are referred to as *cradle cap.* Seborrheic dermatitis has a predilection for areas with a high density of sebaceous glands, such as the scalp, face, ears, presternal chest, penis, and intertriginous areas, including the folds of the diaper region (Figure 138.1B). The red or pink papules and plaques may have a greasy quality. Secondary infections may occur with *Candida,* particularly in the intertriginous areas. Seborrheic dermatitis is usually not exceedingly pruritic, in contrast with atopic dermatitis. The intertriginous involvement and the onset shortly after birth may help to differentiate between these 2 dermatitides. Severe seborrheic dermatitis may be associated with an immune deficiency, such as HIV.

Irritant or *allergic contact dermatitis* occurs when individuals come into physical contact with an irritant or a specific allergen, respectively. Irritant dermatitis is caused by direct cytotoxic effect, while allergic contact dermatitis is a delayed type of hypersensitivity (ie, type IV hypersensitivity reaction) in response to an allergen. Although their etiologies are different, the 2 typically have a similar clinical appearance, with well-defined erythematous vesicles, papules, or plaques, often with scale, oozing, and subsequent lichenification. Diaper dermatitis is among the most common types of irritant dermatitis in the pediatric population (see Chapter 137).

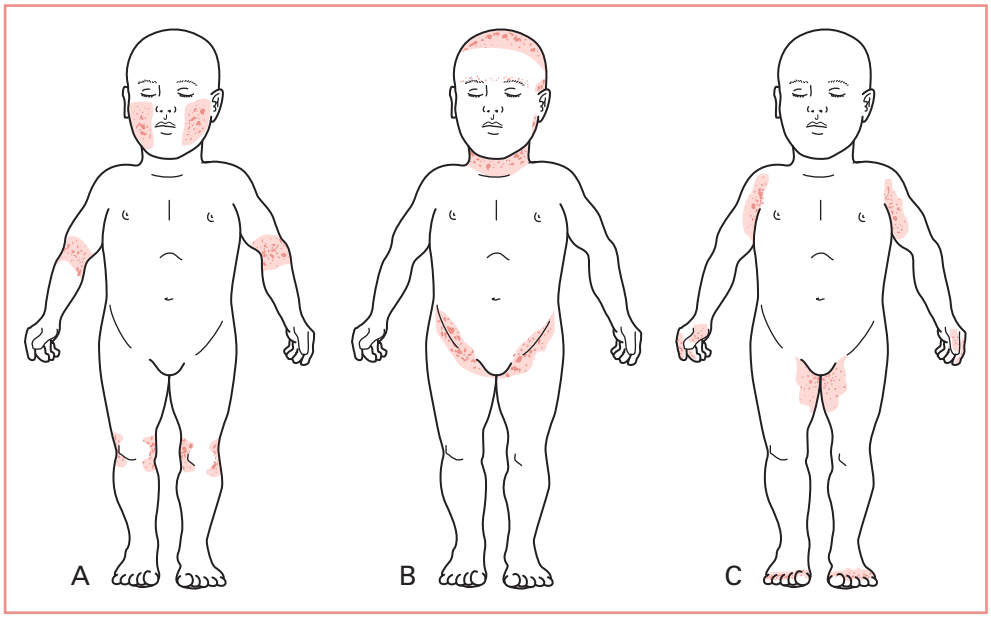

Figure 138.1. Typical distribution of papulosquamous eruptions in children. A, Atopic dermatitis: usually located on cheeks, creases of elbows, and knees. B, Seborrheic dermatitis: usually located on scalp, behind ears, in thigh creases, and behind eyebrows. C, Scabies: usually located on axillae, webs of fingers and toes, and intragluteal area.

Rhus dermatitis (poison ivy/oak), nickel, and fragrance allergy are among the common types of allergic contact dermatitis seen in older children and adolescents. Sensitization to allergens can begin by around 6 months of age. It remains controversial whether atopic dermatitis is a risk factor for allergic contact dermatitis. However, children with atopic dermatitis may have more exposure to sensitizers, in conjunction with a damaged epithelial barrier, putting them at risk.

Plaque-type psoriasis, a chronic papulosquamous skin condition manifested most commonly as well-defined erythematous papules and plaques with silvery scale, is not uncommon in childhood. About 40% of adult patients with psoriasis report having had the disease in childhood. It most commonly affects the scalp in the pediatric population as well as the face and intertriginous areas. Infrequently, a young infant may develop psoriasis in the diaper area. Guttate psoriasis features smaller scaly papules and is usually precipitated by group A streptococcal infection in the pharynx or perianal area. Pruritus is variable but not prominent. Classically, psoriatic lesions can develop at sites of trauma (scratches and cuts), known as the Koebner phenomenon. Given that psoriasis is an inflammatory skin condition, clinicians should screen pediatric patients with psoriasis for associated comorbidities, including metabolic and lipid abnormalities, in addition to signs and symptoms of arthritis, depression, and anxiety.

Pityriasis rosea is a self-limited papulosquamous eruption that is frequently seen in adolescents. The lesions tend to be round or ovoid and classically have a symmetric distribution on the trunk extending downward from the midline at a 45° angle, a pattern resembling a pine tree on the back. Classically, there is a larger herald patch preceding the eruption by a few days to weeks. However, the presentation is not always classic; many patients cannot recall a herald patch, and the pattern over the trunk may be haphazard. Pityriasis rosea is generally self-limited and resolves in 1 to 2 months. It is pruritic in about one-quarter of those affected. The etiology is unknown, although some report an association with human herpesvirus 6 or 7 infection.

Lichen planus is an uncommon papulosquamous eruption in the pediatric population, most frequently afflicting children of Arab and Afro-Caribbean backgrounds. It is characterized by pruritic, polygonal, pink to purplish flat-topped papules, sometimes with an overlying network of delicate white lines called Wickham striae. Etiology is also unknown, although viruses, including hepatitis C, and medications can occasionally be associated. Flexor surfaces are usually affected, and these lesions can koebnerize. Lichen planus affecting the skin typically resolves within 1 to 2 years; meanwhile, lichen planus involving the mucous membranes and nails, albeit rare in children, may persist.

Lichen striatus is an asymptomatic eruption consisting of flat-topped papules that are skin colored to slightly hyperpigmented. The lesions develop along the Blaschko lines and may be arranged in a curvilinear distribution. This eruption spontaneously resolves over months to years. It is most commonly seen between 9 months and 9 years of age. The etiology is unknown, although up to 85% of individuals with lichen striatus report a personal or family history of atopy.

Scabies may resemble atopic or seborrheic dermatitis in infants and young children. The lesions may be papules, pustules, or vesicles. The characteristic burrow, which is only 3- to 10-mm (0.1- to 0.4-in) long, is often difficult to appreciate unless certain diagnostic maneuvers are undertaken. The lesions are most often noted on the skin of the hands and feet, including the palms and soles in infants and young

children. Intertriginous areas, such as the intragluteal region, groin, and finger webs, are commonly infected (Figure 138.1C). In infants and those who are immunocompromised, all skin surfaces, including the face and head, may be involved. Scratching and secondary infection may alter the appearance of the rash. Reddish-brown nodules may be characteristic of more chronic infection. In individuals who are institutionalized or immunosuppressed, extensive mite infection can occur, resulting in thick, greasy-appearing, yellowish scale and crusts over the extremities and trunk, a condition referred to as *crusted scabies.* The use of long-term topical corticosteroid use has been reported to induce crusted scabies.

Fungal infections (eg, tinea corporis, tinea pedis) commonly appear as papulosquamous eruptions. The lesions usually assume a characteristic morphology, with scaly papules grouped in a circle or coalesced into an annular plaque with central clearing.

Evaluation

History

A thorough history should be obtained (Box 138.2). The presence of a rash in other family members is suggestive of a contagious condition such as scabies or a familial disorder such as atopic dermatitis or psoriasis. An onset in the first few weeks after birth is consistent with seborrheic dermatitis. It is important to determine if any medications have been used because these may modify the appearance of the rash. In addition, certain medications can cause a rash themselves, although these tend to be more morbilliform in appearance (see Chapter 139). Pruritus should be noted. Asking about lesions developing at sites of previous trauma can aid in diagnosing eruptions that koebnerize, such as psoriasis and lichen planus.

Physical Examination

The physical examination helps define the exact nature of the eruption and its distribution, which is often the clue to its etiology. The entire body should be examined, and particular attention should be paid to the intragluteal region and web spaces between fingers and toes. Certain rashes have characteristic appearances. For example, a circular cluster of scaly papules with central clearing signifies tinea corporis, whereas the presence of a herald patch preceding a more generalized eruption can suggest pityriasis rosea. The presence of burrows characterizes scabies. Burrows appear as a 3- to 10-mm (0.1- to 0.4-in) grayish-white line (only about 1 mm [0.04 in] wide). Vesicles, pustules, and nodules may also be present in scabies.

It is important to distinguish if any secondary lesions, such as linear excoriations, are present. Secondary infections are also important to diagnose and treat because they can complicate many of the papulosquamous eruptions.

Associated cutaneous features can also aid in diagnosis. Hyperlinear palms, keratosis pilaris (erythematous 1- to 2-mm [0.04- to 0.08-in] folliculocentric papules often on lateral upper arms, anterior thighs, and cheeks), and perioral or periocular lichenified papules are often seen in children with atopic dermatitis.

Overall health, including height and weight, should be assessed. Failure to thrive in conjunction with eczematous skin changes should raise suspicion for an immunodeficiency.

Box 138.2. What to Ask

Papulosquamous Eruptions

- How long has the child had the rash?
- What did the rash look like when it first appeared?
- Are other family members affected?
- Have any medications been used to treat the rash or any been given prior to the onset of the rash?
- Is pruritus present?
- Does the child have any other symptoms, such as wheezing or rhinorrhea?
- Does the child have a history of any contact between the affected skin and any irritating substance?
- Has the child been febrile?

Laboratory Tests

Certain diagnostic tests may help clarify the etiology of certain papulosquamous eruptions. In children with atopic dermatitis, approximately 30% may have coexisting food allergies and 70% may have coexisting respiratory allergies. Food allergies tend to develop during early infancy, whereas respiratory allergies may develop during childhood. While it is important to identify food (and later on, environmental) allergies via skin or radioallergosorbent/ImmunoCAP testing, which measures allergen-specific IgE (see Chapter 95), parents must understand that food allergies infrequently cause or exacerbate atopic dermatitis. Patients with atopic dermatitis often have elevated IgE antibodies on testing and may be incorrectly diagnosed with a food allergy. A positive skin or blood test result does not imply a true food allergy unless it is clinically confirmed with a food challenge test. Based on misperceptions on the role of food allergies in atopic dermatitis, parents may, on their own, institute dietary restrictions for their child, which often results in gross undertreatment of the skin itself and may even lead to dangerous levels of malnutrition. This unwarranted dietary restriction may also lead to an unintended loss of tolerance of foods, resulting in a higher risk of reactions. Therefore, proper referral and counseling are especially important in infants who have atopic dermatitis and food allergies. Atopy patch tests can be used to detect positive aeroallergens, with dust mites being the most commonly implicated and clinically relevant culprit. Patch testing may identify allergens causing contact dermatitis. Serologic IgE may or may not be elevated in children with atopic dermatitis.

The burrow of the mite that causes scabies may not be readily apparent. Scrapings with mineral oil help identify the mite, eggs, or feces (scybala)—any of these are diagnostic. Multiple burrows or web spaces are scraped. Scrapings of skin also assist in diagnosing candidal or tinea infections. These scrapings should be mixed with 10% to 20% potassium hydroxide, which facilitates the dissolution of epithelial debris and allows for identification of the spores or hyphae.

If a secondary bacterial infection is suspected, cultures of the skin are indicated. Most papulosquamous eruptions are diagnosed clinically and no other specific diagnostic tests, short of a skin biopsy, assist in the diagnosis.

Management

Management is determined by the diagnosis.

Management of atopic dermatitis hinges on skin barrier function and the reduction of dryness and irritation with vigilant skin care. There has been debate whether frequent short baths daily versus bathing infrequently is more beneficial. It is most crucial that these patients bathe for short times only, applying cleansers only to the face, groin, and other soiled areas. The cleanser should be soap free, or the soap should be nonirritating, nondrying, and perfume and dye free. The skin should be patted dry after bathing with immediate application of emollient or medication. Thick emollients, such as petroleum jelly or other greasy ointments, are preferable. For school-age children, using greasier emollients at night under pajamas and thinner emollients during the day may increase compliance. Avoiding scratchy clothing such as wool can be helpful, as can humidifiers in the winter to prevent excessive environmental dryness. Humidifiers should be cleaned regularly to prevent mold buildup, and a cool mist is considered safer to prevent burns. Effective strategies to reduce house dust mite burden, including bedding covers and vacuuming, may lead to a modest improvement of atopic dermatitis symptoms.

Topical steroids are used to treat various papulosquamous eruptions, especially during flares. These are the mainstay of therapy designed to minimize inflammation. The agents usually prescribed in cases of atopic as well as seborrheic dermatitis are triamcinolone 0.025% or 0.1% and hydrocortisone 1% creams or ointments. Although ointment vehicles allow for better penetration and, often, less irritation, they are often disliked for their greasy texture, minimizing their usefulness because they are not applied regularly. The weaker topical steroids (eg, hydrocortisone) should be used for the face and groin and the higher strengths (eg, triamcinolone) in areas of thicker skin. Chronic use should be discouraged to avoid skin atrophy. Parents can be educated on applying the medication to the appropriate areas for 1 to 2 weeks for flares, with maintenance use on weekends or a few days per week. Sometimes brief courses of systemic steroids may be needed during more severe exacerbations, but if a patient is requiring oral steroids regularly, a referral to a dermatologist may be needed to consider other treatments, such as systemic immunomodulators or UV therapy, both of which are used for atopic dermatitis and psoriasis. Oral steroids may be required for rhus contact dermatitis, which is among the more common forms of allergic contact dermatitis, and should be given for 2 to 3 weeks to prevent flaring.

For scaly scalp psoriasis, seborrheic dermatitis, and atopic dermatitis, several treatments can be used. For pruritus and inflammation, a topical steroid in gel, liquid, oil, or foam vehicle can be applied. Mineral or baby oil can help loosen scale, which can be washed out using a gentle shampoo or antiseborrheic shampoo. It should be massaged gently onto the scalp and allowed to sit for several minutes before rinsing.

Tacrolimus and pimecrolimus are topical calcineurin inhibitors, which can be used as steroid-sparing agents, most often in mild cases of atopic dermatitis, seborrheic dermatitis, and inverse (intertriginous) psoriasis. Dermatologists, allergists, and immunologists prescribe these medications in conjunction with topical steroids for their patients. As stand-alone agents, they are not as effective as steroids for more severe cases and are substantially more expensive. As of January 2006, a black box warning was placed on these 2 medications because of theoretical risks of skin cancer and lymphoma among patients using these drugs. The warning was based on the risk in transplant patients who are on systemic calcineurin inhibitors. One cohort study showed an association between the use of topical tacrolimus and the development of B-cell acute lymphoid leukemia in pediatric patients with atopic dermatitis. However, multiple epidemiological studies showed no evidence that topical calcineurin inhibitors are associated with increased risk for developing malignancies such as skin cancer and lymphoma.

In 2016, the US Food and Drug Administration approved the use of crisaborole (trade name Eucrisa) as a topical nonsteroidal treatment for mild to moderate atopic dermatitis in patients 2 years of age and older. There are also ongoing clinical trials on its potential role as a treatment for psoriasis. In 2017, the US Food and Drug Administration approved the use of the first biologic medication, dupilumab (trade name Dupixent), a monoclonal antibody, as an injectable treatment for moderate to severe atopic dermatitis in adults. The safety of this medication for use in the pediatric population is currently being investigated.

In psoriasis, topical steroids are often used in conjunction with calcipotriene ointment or cream. Tar and anthralin are still used as adjunctive topical treatments, although they are falling out of favor due to their messy quality and more favorable alternatives. Systemic agents, including biologic drugs, are also used in the treatment of moderate to severe psoriasis. In 2016, etanercept (trade name Enbrel) was the first biologic to be approved for pediatric plaque psoriasis.

Antihistamines may play a role in reducing pruritus, especially at bedtime, due to their sedating effect. Hydroxyzine and diphenhydramine work well in the evenings. For daytime, fexofenadine hydrochloride, cetirizine hydrochloride, and loratadine are less-sedating choices. Regular use of antihistamines during a flare can help to break the itch-scratch cycle often observed in children with atopic dermatitis. The other conditions can have variable degrees of pruritus for which antihistamines can be useful. Clipping fingernails decreases the risk of skin trauma after scratching.

Antibiotics are indicated if secondary infection is present. The most common pathogen involved is *Staphylococcus aureus*. Staphylococcal antigens also exacerbate the inflammation of atopic dermatitis. Treatment with antistaphylococcal systemic antibiotics such as cephalosporins may be needed for more widespread secondary infections. Topical antibiotics such as mupirocin may be used in localized secondary infections. Streptococcal-associated guttate psoriasis should also be treated with appropriate antibiotics.

Seborrheic dermatitis is generally treated with a combination of products, including topical keratolytics, corticosteroids, and antifungals (see Chapter 136). The seborrheic dermatitis of infancy can be treated with topical shampoos containing selenium sulfide and gentle sloughing of the scaly lesions using a soft brush or cloth. Topical calcineurin inhibitors have anti-inflammatory properties without skin atrophy side effects but are generally reserved for periorbital or recalcitrant cases because of the cost of the medications.

Atopic dermatitis can be complicated by infection with herpes simplex (eczema herpeticum), in which case treatment should be initiated with acyclovir. Involvement of the periorbital skin or nasal tip is concerning for eye involvement and warrants an ophthalmologic consultation. If involvement is severe, the patient may need to be hospitalized for intravenous antiviral therapy. Children with atopic dermatitis are also prone to viral infections resulting in warts and molluscum contagiosum; these should be managed accordingly.

Coinfection with *Candida,* which occurs with seborrheic dermatitis and psoriasis, requires the use of topical medications such as nystatin, clotrimazole, or miconazole. Antifungal shampoos may also help in reducing the scaling due to fungal agents such as *Malassezia.* Tinea corporis responds to topical antifungal agents. Tinea capitis requires administration of systemic antifungals (see Chapter 136).

The treatment for pityriasis rosea remains controversial, especially because it is a self-resolving condition. There are several studies demonstrating effectiveness of acyclovir, erythromycin, or UV therapy to speed recovery.

Several medications are used to treat scabies. Currently, the preferred product is 5% permethrin cream. It is approved for infants 2 months or older, although its safety and efficacy has been reported in a 23-day-old. It should be applied from head to toe in infants and from neck to toe in small children and adults, left on for 8 to 12 hours, then rinsed off. Lindane, which has been used for more than 50 years and was previously used worldwide, is a 1% cream. Because of concern about the percutaneous absorption of lindane and its potential neurotoxicity, it is no longer widely used and is not available in some areas. Oral ivermectin is also a successful scabicide. A single dose of 200 mcg/kg, repeated in 1 week, can be used in children weighing more than 15 kg (>2.2 lb) and women who are not pregnant or breastfeeding. All scabicides should be readministered 7 days after initial treatment. Patients with crusted scabies typically require a combination of permethrin with oral ivermectin; addition of salicylic or lactic acid can improve the hyperkeratosis. The effective elimination of scabies necessitates that all affected household members be treated simultaneously and that bed linens and clothing be washed in hot water. Patients should be warned that the pruritus of scabies often takes several weeks to subside and can be treated supportively with steroids and antihistamines.

Prognosis

In general, the prognosis for children with papulosquamous eruptions is excellent with appropriate management, for which accurate diagnosis is critical. Atopic and seborrheic dermatitis usually improve as children get older. However, chronic problems such as hand dermatitis, which can be exacerbated by occupational exposures, can become a significant problem in patients with atopic dermatitis. Children with significant atopic dermatitis should be counseled to avoid prolonged contact with water. People with occupations with frequent handwashing or contact with water, such as hairdressers, hospital workers, and food service workers, are at increased risk of hand dermatitis. It is also critical to manage the expectations of the patient and family, in that completely clear skin is not the primary goal of treatment. Rather, the primary goal is prevention of flares with a good skin care maintenance regimen. Families of children with severe atopic dermatitis can have difficulty in maintaining a good quality of life for these patients, and the entire family structure can be affected, as chronic care can be challenging. Children with atopic dermatitis frequently experience remissions and exacerbations, particularly associated with seasonal changes. Prevention and maintenance must be stressed. It is advisable that patients with recalcitrant eczema have further workup with an allergist to identify potential triggers.

Many of these eruptions, such as lichen striatus and pityriasis rosea, are self-limited and only need symptomatic treatment. Psoriasis has a more chronic course, and early diagnosis and treatment can help to reduce disease severity and progression. Chronic disease such as atopic dermatitis and psoriasis can be psychologically challenging for children because they can often be ridiculed at school and excluded from activities for unfounded fears of contagiousness. It may be necessary to educate teachers as well and provide emotional and psychological support for these children. Clinicians may also screen for depression and anxiety, with tools such as the Patient Health Questionnaire (www.phqscreeners.com).

Scabies and tinea will improve with appropriate management and education to prevent recurrence.

CASE RESOLUTION

The infant's presentation is characteristic of seborrheic dermatitis. The baby experienced the onset of symptoms as a young infant (most atopic patients develop symptoms after 2 months of age). Seborrheic dermatitis can often affect the head and face of young patients. Xeroderma is also apparent.

The most important topic to discuss with the mother is good skin care. The mother should be advised that although she may use the baby oil to loosen the scale on the scalp, she should shampoo afterward with a mild antiseborrheic shampoo to prevent buildup. A mild topical steroid, such as hydrocortisone 1% ointment, may also be recommended, although chronic use should be dissuaded. If skin scrapings reveal secondary infection with *Candida,* an antifungal cream should be added to the regimen; if a secondary bacterial infection is suspected, a culture should be taken and treatment with topical or systemic antibiotics initiated. Short baths with a mild cleanser and regular application of emollients are critical.

The mother should also be educated on potential flares with vaccinations and infections, as well as with climate changes. It is important that the infant catch up on her vaccinations, but cautioning the mother about a potential flare can prevent concern.

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CHAPTER 139

Morbilliform Rashes

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CASE STUDY

A 10-month-old girl is brought to the clinic with a history of rhinorrhea, cough, and fever for 3 days prior to the onset of a confluent, erythematous rash. The rash started on her face. She has been irritable, and her eyes are red and teary. Her immunizations include 3 sets of diphtheria, tetanus, and acellular pertussis; polio; rotavirus; *Haemophilus influenzae* type b; conjugated pneumococcal; and hepatitis B vaccines. No one at home is ill. The girl was seen in the emergency department 2 weeks earlier because she caught her finger in a car door. On physical examination, the girl's temperature is 39°C (102.2°F). A confluent eruption of erythematous macules and papules is evident on the face, trunk, and extremities. Rhinorrhea and conjunctivitis are also present.

Questions

1. What are the common causes of febrile maculopapular or morbilliform rashes in children?
2. What features help the differential diagnosis of morbilliform rashes?
3. How does a child's nutritional status affect the child's reaction to certain exanthem-inducing viruses?
4. What are the public health considerations concerning viral exanthems in children?

Exanthems are skin findings resulting from an underlying disease, most often caused by a viral infection, although in a few cases, they may be due to bacteria or other rare pathogens. In children, these exanthems are most commonly macular, papular, or mixed. The rash of measles is described as *morbilliform,* and this adjective is used to describe similar-appearing eruptions of macules and papules. Frequently, these rashes present in conjunction with fever, and additional nonspecific symptoms include myalgia, rhinorrhea, conjunctivitis, headache, gastrointestinal (GI) symptoms, and lymphadenopathy. Rarely, other internal organs, such as the liver, spleen, lung, heart, and central nervous system (CNS), are also damaged in serious cases. The exanthems of various underlying pathogens can also be seasonal and have unique presentations. Although many of the common childhood illnesses of the past are now prevented by immunizations, not all segments of the population are adequately immunized. In addition, some children are not eligible for immunization because of their young age. Allergic reactions to medications, particularly antibiotics, may also result in similar eruptions and can be accompanied by symptoms of low-grade fever and pruritus. Differentiating viral exanthems from allergic reactions may be difficult in febrile children who have been empirically started on antimicrobial agents.

Epidemiology

In most children, viruses that cause exanthems produce mild disease without significant morbidity or long-term sequelae. Of greater concern to the public health is the risk of potential spread through the population. Morbilliform eruptions are a common presenting symptom, particularly in certain age groups and at certain times of the year.

Measles, also known as rubeola, is caused by an RNA virus and has markedly decreased in the United States since the live vaccine was introduced in 1963. It is transmitted by direct contact with infectious droplets or by airborne spread. In temperate climates, it is most frequently seen in the winter and spring. In the pre-vaccine era, measles was a significant cause of morbidity and mortality. Periodic resurgences have occurred, particularly among unimmunized preschoolers, older adolescents, and young adults. In addition, young infants are also at risk because of decreased levels of passively transferred maternal immunity related to lack of maternal natural infection or immunization. Vaccine-related immunity apparently wanes more rapidly in mothers than does naturally acquired immunity. Because of the increased number of cases in preschoolers and children with primary vaccine failure who received the vaccine appropriately, a 2-dose recommendation by the American Academy of Pediatrics was implemented in 1989, although there continue to be cases each year. Although no longer endemic in the United States, decreasing vaccination rates have resulted in an increased risk for outbreaks of previously eradicated infectious diseases, specifically measles. The incubation period of measles is about 10 days. Individuals are infectious from about 3 to 5 days before the onset of rash until 4 days following its appearance.

Rubella is also caused by an RNA virus and is no longer considered endemic in the United States, with rare cases reported annually. Sporadic outbreaks are reported, generally in foreign-born or under-immunized persons, and the last confirmed endemic case in the Americas was diagnosed in Argentina in 2009. However, about 5% to 10% of US individuals older than 5 years are considered to be susceptible. Peak incidence is in the late winter to spring, and it is likely transmitted via direct or droplet contact from nasopharyngeal

secretions. Although generally a mild disease, its most serious manifestation is congenital rubella syndrome, which may develop in the offspring of infected pregnant women, with the greatest risk of congenital defects during the first trimester. The incubation period is 14 to 23 days.

Erythema infectiosum, also called fifth disease, is most commonly seen in school-age children during late winter to early spring. Most adults have antibodies indicating previous infection. The disease is caused by an acute infection with parvovirus B19, a DNA virus, and spread through respiratory secretions, percutaneous exposure to blood or blood products, and vertical transmission from mother to fetus. The incubation period is generally 4 to 14 days but may be up to 21 days.

Exanthem subitum, also known as roseola infantum, generally affects children from 6 months to 2 years of age, as maternal antibodies are protective until the age of 6 months. The illness is due to infection with human herpesvirus (HHV) 6 or 7, although HHV-6B, a DNA virus, is most commonly the etiologic agent. The virus is shed in the saliva, even among healthy, previously infected individuals. Almost all children are seropositive for HHV-6B by the age of 4 years. Reactivation is possible, although not common, and there is no seasonal pattern. The incubation period for HHV-6 is likely 5 to 15 days and is unknown for HHV-7.

Enteroviruses are the most common cause of exanthems in the summer and fall. They are all RNA viruses of the picornavirus group and include coxsackieviruses (groups A and B), echoviruses, and enteroviruses. Infection is spread through fecal-oral and respiratory routes as well as via fomites. There is also vertical transmission. Infection is more common in young children and people with poor hygiene. The incubation period is usually 3 to 6 days.

Kawasaki disease, an acute self-limited vasculitis, is of uncertain etiology, although an infectious cause is suspected due to epidemics occurring usually in the winter and spring. Most patients are between 6 months and 5 years of age. Males outnumber females by a ratio of 1.5:1. The incidence of the disorder among Asians is higher than in other populations, suggesting genetic factors play a role. The incubation period is unknown.

Gianotti-Crosti syndrome, also known as papular acrodermatitis of childhood, has historically been associated with hepatitis B infection. In the United States, it is believed to be a host response to multiple viral infections including, but not limited to, hepatitis B, Epstein-Barr virus (EBV), parvovirus B19, HHV-6, and the enteroviruses. It is seen most frequently in children 1 to 6 years of age.

Scarlet fever is a cutaneous reaction to several pyrogenic exotoxins produced by group A streptococcus. It is transmitted through respiratory secretions. Scarlet fever is usually seen in young children between 1 and 10 years of age with pharyngitis. It occurs most commonly in cooler climates during the late fall, winter, and early spring. The incubation period is 2 to 5 days.

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii,* an intracellular organism. Infection is transmitted by the bite of *Ixodes* ticks, which are reservoirs and vectors of the organism. It can be seen throughout the United States, with most cases seen in the southern states. Children of any age are at risk, with those 5 to 9 years of age and those not recalling a tick bite, an occurrence in about one-half of pediatric cases, having the greatest mortality. The highest incidence of infection is seen between April and September. The incubation period lasts from 2 to 14 days.

Clinical Presentation

Morbilliform eruptions may involve the face, trunk, or extremities. The eruption is usually erythematous, and the lesions are flat or slightly raised. Occasionally, lesions within the mouth, referred to as enanthema, are evident. Most children are febrile (Box 139.1) and may have other symptoms.

Pathophysiology

The mechanism for development of a rash is variable. In some cases, the rash is the reaction of the body to infection or to the presence of a toxin. In general, the sequence involves exposure to an infectious agent and then acquisition of the agent, most commonly through droplet infection or fecal-oral contamination. The agent, usually a virus, then replicates, perhaps in the reticuloendothelial system. Lymph nodes enlarge, reflecting the involvement of the reticuloendothelial system. Associated viremia may be present.

In Kawasaki disease, vasculitis affects multiple organ systems. Various cytokines and autoantibodies play a role in the inflammatory response. In a toxin-mediated rash (eg, scarlet fever), previous exposure to the toxin is believed to sensitize the individual.

Diagnosis and Differential Diagnosis

While many exanthems can be easily recognized clinically, the decreased frequency of many of these usual childhood diseases means that physicians encounter these conditions less frequently than in the past. Familiarity with the appearance of these conditions is critical to diagnosis. Using a database of pictorial representations can be valuable. Such databases may also have ways to search by features such as rash morphologies, symptoms, exposures, skin color, body location, age, immune status, and many other factors. Morbilliform exanthems are associated with several infectious diseases, such as measles, rubella, erythema infectiosum, roseola, enterovirus infections, Gianotti-Crosti syndrome, Kawasaki disease,

Box 139.1. Diagnosis of Morbilliform Rashes in Pediatric Patients

- Macular, papular, or combined rash
- Fever
- Enanthema (lesions in the buccal mucosa, uvula, and pharynx)
- Lymphadenopathy
- Respiratory symptoms
- Gastrointestinal symptoms

scarlet fever, and RMSF. Drugs can also cause eruptions similar to those caused by the aforementioned diseases.

The rash associated with measles is preceded by the 3 Cs of cough, coryza, and conjunctivitis in addition to fever, which last for several days before the eruption of the exanthem. Lesions on the buccal mucosa, called *Koplik spots*, are well-circumscribed white-gray papules (Figure 139.1) that appear during the prodrome and resolve after 3 to 4 days. This enanthema, although rare, is pathognomonic for measles. The measles rash itself usually begins on the head, particularly behind the ears and around the margin of the scalp, and then spreads cephalocaudally. After 2 to 3 days, the eruption becomes confluent and copper-colored, fades in the order it appeared, and then may desquamate. The greatest morbidity and mortality are seen in individuals who are immunocompromised and malnourished. Complications include secondary bacterial infection, pneumonia, and encephalitis.

Rubella produces a relatively minor illness in children, although adults, particularly women, may experience painful arthritis. Up to one-half of infections are asymptomatic. There can be a prodrome of fever, headache, conjunctivitis, and upper respiratory symptoms. The eruption consists of fine erythematous macules and papules that become near confluent, starting on the face and progressing caudally to the trunk, resolving after 3 days. Lymphadenopathy, particularly of the postauricular or suboccipital nodes, is characteristic of the disease. *Forchheimer spots* are pinpoint rose-colored macules that can develop on the soft palate in patients with this infection. Congenital rubella syndrome results in multisystem anomalies that can follow maternal infection and is part of the TORCH congenital infections (toxoplasmosis, other agents [syphilis, hepatitis B, varicella-zoster virus, human immunodeficiency virus (HIV), parvovirus B19, enteroviruses, lymphocytic choriomeningitic virus], rubella, cytomegalovirus, and herpes simplex virus).

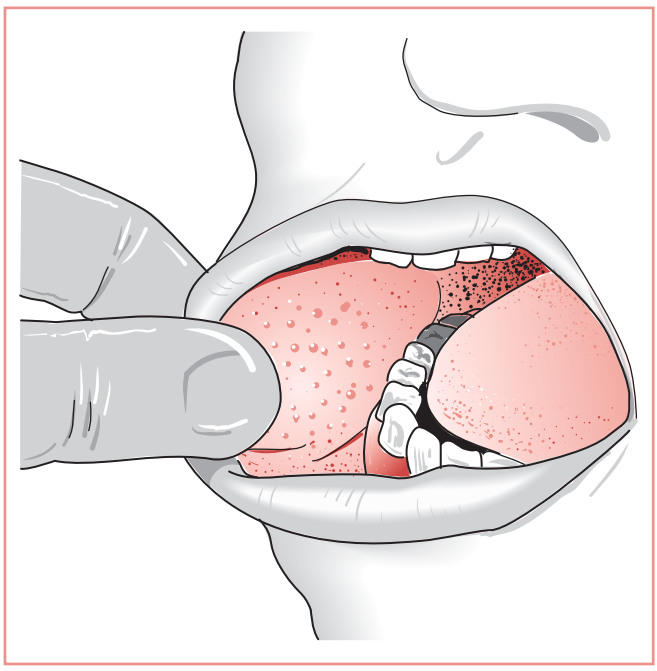

Figure 139.1. Koplik spots.

Erythema infectiosum is characterized by a distinctive eruption that may be preceded by mild prodromal symptoms, including low-grade fever, headache, myalgia, and malaise. Eruption generally occurs 7 to 10 days after the prodrome. The facial rash consists of erythematous patches on the cheeks with sparing of the nasal bridge and periorbital areas. This "slapped-cheek" appearance generally fades after several days and is considered the first stage of the illness. In the second stage, the extremities may develop a lacy reticulated rash of macules and papules 1 to 4 days later that can be pruritic. Palm and sole involvement are rare. This usually lasts about a week but may have recurrences over several weeks in the third stage, with triggers such as activity, sunlight, emotional stress, and hot baths. Most children are only mildly ill and may attend school, but children with underlying hematologic disorders may experience aplastic crises because of the affinity of parvovirus B19 for developing red blood cells. Children who are immunocompromised are also at risk for chronic anemia. Pregnant females may transmit this infection to their fetuses, which can result in fetal hydrops, growth retardation, anemia, isolated pleural and pericardial effusions, high-output congestive failure, and fetal loss. Adults with parvovirus infection frequently develop arthritis, although only 10% of children experience this symptom. Neurologic disturbances, including encephalitis and neuropathies, may follow parvovirus infection, although this is rare. *Papular-purpuric gloves-and-socks syndrome* is a self-limited acute eruption linked to parvovirus B19 infection. It usually occurs in the spring and summer, characterized by often-pruritic edema and erythema and progressing to purpuric macules and papules with a sharp line of demarcation at the wrists and ankles. A nonspecific enanthema of petechiae and erosions can occur. Symptoms of myalgia, lymphadenopathy, anorexia, and fatigue may follow the rash. The exanthem generally resolves after 1 to 2 weeks with no residual sequelae.

Exanthem subitum (roseola infantum) usually causes a fairly mild illness in children, although there can be associated complications. Defervescence usually accompanies the rash, which consists of fine, non-pruritic, blanchable, pink macules or papules with a surrounding halo that generally appear first on the trunk and then spread centrifugally. Some affected individuals may develop an enanthema consisting of erythematous papules on the soft palate and uvula called *Nagayama spots*. Periorbital edema can also be seen. On average, the rash evolves over 12 hours and usually resolves by 2 days. Infants may appear sickest during the prodromal phase, when fever is high (temperature often ≥39.5°C [≥103°F]), and infants are irritable as a result. Fever generally lasts 3 to 5 days and can be accompanied by upper respiratory symptoms and lymphadenopathy. Seizures during the febrile period can occur in up to 15% of primary infections. Workup to rule out sepsis is often warranted.

Skin eruptions associated with enterovirus infections are highly variable. They may be distinct and characteristic, such as hand-foot-and-mouth disease, most commonly associated with coxsackievirus A16 and enterovirus 71 (see Chapter 140). However, many of the enteroviral exanthems are less distinctive and have a generalized morbilliform appearance. Neurologic complications associated

with enteroviral infections include aseptic meningitis and encephalitis and have been reported in infections with coxsackievirus B and enterovirus 71. Other systems affected by enteroviral infections include respiratory, GI, ophthalmic, and cardiac. In a 2011–2012 North American outbreak caused by coxsackievirus A6, affected individuals had distinctive skin findings mimicking eczema herpeticum (see Chapter 140), as well as Gianotti-Crosti syndrome-like rash and petechial or purpuric eruptions.

The rash of Kawasaki disease is also highly variable; it may be morbilliform, urticarial, or scarlatiniform or resemble erythema multiforme. During the first week of illness, there may be desquamation of the perineum. The diagnosis of Kawasaki disease requires fever (generally temperature >39.0°C [>102.2°F] lasting at least 5 days) and 4 out of the following 5 findings: bilateral non-purulent conjunctivitis; changes in the oropharyngeal mucosa including fissured lips, oral erythema, and strawberry tongue; changes in the extremities such as erythema/edema or desquamation; cervical lymphadenopathy with 1 node measuring at least 1.5 cm (0.2 in) in diameter; and the exanthem described previously. Irritability, arthralgia, abdominal pain, and diarrhea are not uncommon. Incomplete Kawasaki disease can be diagnosed when only 2 of the additional criteria are met; thus, the health professional should consider this diagnosis when persistent high fever and only 2 or 3 of these symptoms are present. The major complication of Kawasaki disease is coronary artery abnormalities, and males and those younger than 12 months are at increased risk.

The exanthem of Gianotti-Crosti syndrome consists of monomorphic, pink- to skin-colored, usually non-pruritic papules on the face, buttocks, and extremities, with sparing of the trunk. There is often a prodrome of fever and upper respiratory symptoms with associated generalized lymphadenopathy and hepatosplenomegaly. The exanthem fades after 2 to 3 weeks but can last up to several months.

Scarlet fever is primarily a disease of childhood. Onset is marked by sudden high fever, headache, vomiting, malaise, and sore throat. Within 12 to 48 hours, erythema develops on the neck, chest, and axillae. The rash quickly becomes generalized to a sandpaper-like rash of fine red papules on an erythematous background. Linear accentuation in the axillary, antecubital, and inguinal folds is known as Pastia lines. The face is flushed, except around the mouth (circumoral pallor). There is pharyngeal injection with exudate developing after a few days. The tongue is initially white with prominent red papillae (Figure 139.2), known as strawberry tongue. As the scarlet fever rash resolves, desquamation begins in 7 to 10 days, lasting up to 6 weeks.

The rash of RMSF begins as blanchable pink macules or papules that evolve into petechial or purpuric non-blanching lesions. They begin on the wrists and spread centripetally. The palms and soles are almost always involved. Exanthem is preceded by symptoms of fever, headache, and malaise. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea can be present. The rash generally develops 2 to 3 days after the prodrome.

Morbilliform rashes are the most common type of cutaneous drug eruption. The most common culprits include sulfonamides, penicillins, cephalosporins, and anticonvulsants. They generally begin as erythematous macules and papules on the trunk that spread to the extremities symmetrically. There is usually concurrent eosinophilia. Pruritus and low-grade fever can also be present, often confounding the diagnosis. Although most drug rashes begin 1 to 2 weeks after starting a drug, an eruption may develop after a drug has been discontinued. After stopping the offending medication, the rash usually resolves over 1 to 2 weeks, but some individuals show improvement even if the offending medication is continued. The underlying pathogenesis of many of these drug rashes continues to be unclear; however, recent studies found that levels of a soluble fatty acid synthetase ligand were increased in patients with drug-induced morbilliform eruptions, as well as in those with toxic epidermal necrolysis, but negative in those with viral exanthems.

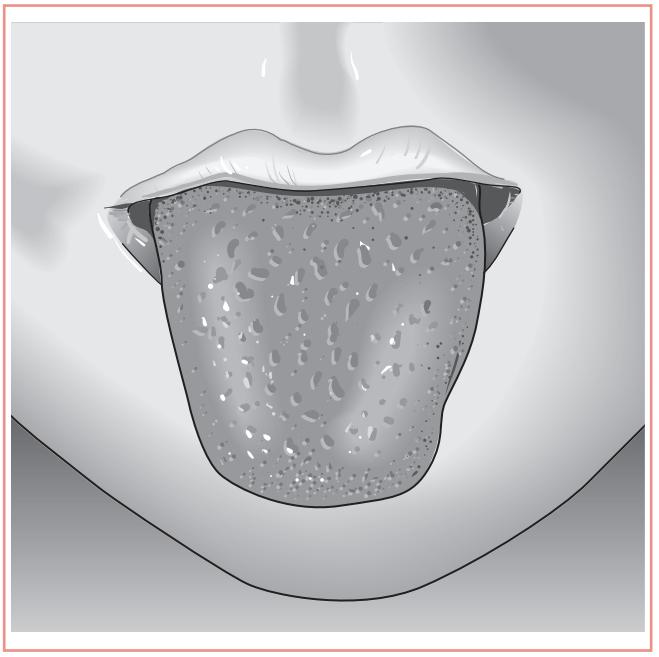

Figure 139.2. Strawberry tongue.

Infection with EBV is associated with rash in young children and in adolescents on antibiotics, usually ampicillin or amoxicillin. Eruption is morbilliform, and the lesions may be erythematous or copper-colored. Fever, upper respiratory symptoms, lymphadenopathy, hepatosplenomegaly, and facial and peripheral edema, including unilateral periorbital edema, may be noted. The rash is likely due to an immunologic interaction between the infectious agent and the drug.

Evaluation

History

A thorough and detailed history should be obtained, including characteristics of the skin rash, the progression of areas involved, overall distribution, and the relationship with rash and other symptoms such as fever. This will be very helpful to make the correct diagnosis (Box 139.2).

Box 139.2. What to Ask

Morbilliform Rashes

- What does the rash look like? Has a similar rash occurred before?
- What is the order of progression of the rash? Are lesions in the mucosa?
- What symptoms, if any, are associated with the rash or occurred before the onset of rash?
- How long has the child had these symptoms?
- Is the child taking any medications (antibiotics)?
- Does the child have any ill contacts?
- What is the child's immunization status?

Physical Examination

The focus of the physical examination is to help define the characteristics of the eruption, such as location, extent, and degree of coalescence. The presence of any associated physical findings, such as fever, lymphadenopathy, enanthema, desquamation, rhinorrhea, conjunctivitis, organomegaly, or CNS symptomatology, should be determined.

Laboratory Tests

Laboratory assessment may be helpful in certain conditions, although most of these diagnoses are made clinically. Serologic testing is most valuable for defining a community outbreak of a specific disease such as measles. In most viral exanthems, the results of serologic studies are not available until the condition has resolved and the patient has recovered. Tests may include acute and convalescent titers for specific viruses. Alternatively, immunoglobulin (Ig) M levels of antibodies against certain infections may be used to document that the infection was recent. Repeat testing may be needed for partially immunized individuals. Polymerase chain reaction may also be useful. Isolating the virus can confirm the diagnosis but is often difficult to obtain. Because neutropenia and lymphocytosis characterize many viral illnesses, such findings are not helpful in differentiating specific causal agents. Lymphocytosis, with characteristically atypical lymphocytes, distinguishes EBV infection. Although a heterophil antibody test result is usually positive in older children and adolescents, the test may be nonreactive in young children, in whom infection is documented by specific EBV serology.

Pregnant women with suspected parvovirus B19 infection should have IgM and IgG levels drawn. If infection is confirmed, serial ultrasonography should be performed to monitor for symptoms of fetal hydrops. Confirming diagnosis of rubella in a pregnant woman is also important because of the potential risk of congenital rubella syndrome.

Kawasaki disease is associated with elevation in markers of inflammation, including leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate, and C-reactive protein, although no test is diagnostic. Sterile pyuria is noted in 70% of the cases. Scarlet fever is characterized by leukocytosis. Eosinophilia can also be seen after a few weeks in up to 20% of patients. Laboratory confirmation, via rapid streptococcal test or throat culture, should be done to confirm that the pharyngitis is caused by group A streptococcus, not a virus. If pharyngitis has resolved, serologic studies such as antistreptolysin O provide evidence of the recent infection.

A 4-fold or greater change in titer between acute and convalescent serum as determined by indirect immunofluorescent antibody assay is diagnostic for RMSF. Many patients will have thrombocytopenia, leukopenia, anemia, and hyponatremia. In general, any child presenting with headache, fever, and possible exposure to tick bite should be evaluated for this disease.

Imaging Studies

Echocardiography to check for evidence of coronary artery aneurysm is a mandated part of the evaluation in Kawasaki disease during the acute phase and with serial repeat examinations, more frequently and earlier in those at high risk in the face of a normal initial echocardiogram.

Management

Management of most viral exanthems is supportive and symptomatic. Hydration is critical when GI symptoms such as vomiting and diarrhea are present. Antihistamines should be used for symptoms of pruritus in addition to regular use of emollients. Painful oral lesions can be treated with topical analgesics. In cases in which complications such as encephalitis or pneumonia develop, hospitalization is indicated. Spread of infection, such as measles, to susceptible contacts can be reduced through the use of vaccine within 72 hours of exposure or Ig within 6 days. Measles vaccine should be administered after the Ig in children who have been exposed, with the time interval dependent on dose received and age of the child. The measles, mumps, and rubella vaccine is administered for the 2-dose vaccine series to children at 12 to 15 months of age and again at 4 to 6 years of age. Measles, mumps, rubella, and varicella (MMRV) vaccine is available for children 12 months to 12 years of age in the United States, although there is greater risk for febrile seizures with MMRV vaccine. HIV infection is not a contraindication to measles vaccination, unless the patient is severely immunocompromised, but MMRV vaccine should not be administered to these individuals. Currently, administration of vitamin A is recommended to all children with measles regardless of their country of residence. Antibiotic therapy should be initiated if bacterial coinfection is suspected but should not be started empirically. The management of Kawasaki disease includes the administration of intravenous Ig and aspirin, which should be started within 10 days of onset of fever. The current recommendation is to administer a single dose at 2 g/kg given as an infusion over 10 to 12 hours. Periodic echocardiography is also required in these patients, with close monitoring by a cardiologist.

If there is a concern for hepatitis in patients with Gianotti-Crosti syndrome, workup should be initiated.

Control measures are important because most morbilliform exanthems are due to infectious agents. Children with postnatal rubella should be kept from school or child care facilities for 1 week after onset of rash. Those with congenital rubella syndrome are

considered contagious for 1 year, and caregivers must be educated. Females receiving rubella vaccine should not become pregnant for 28 days following vaccination. Hand hygiene is an important control measure that should be used to minimize spread of many of these viruses.

Public education about the importance of immunizations is vital to reducing the effect of diseases such as measles and rubella. Although the number of cases in the United States is low, importation of these viruses from other countries mandates continued widespread vaccination. In addition, parental concerns of potential adverse reactions due to vaccinations have led to vaccine refusal by some.

Pregnant women infected with parvovirus B19 with ultrasonography suggestive of fetal hydrops should be referred to a tertiary care facility because intrauterine blood transfusions have proven successful. Routine exclusion of pregnant women from the workplace where erythema infectiosum has been identified is not recommended because the virus is transmitted before the onset of rash and, thus, exclusion is unlikely to be effective. Patients with aplastic crisis and chronic parvovirus infection may be contagious for extended periods and require longer periods of precautions. In addition, patients with papular-purpuric gloves-and-socks syndrome are considered infectious when clinical symptoms of their eruption are present. Patients with aplastic crises may need transfusions, and intravenous Ig has been used successfully in immunocompromised patients with chronic infection. However, most cases of erythema infectiosum do not require absence from school or treatment beyond supportive care.

Intravenous Ig and high-dose aspirin continue to be first-line treatment to decrease the risk of coronary artery aneurysms in patients with Kawasaki disease. Aspirin should be continued indefinitely in patients in whom coronary abnormalities do develop.

The goal of therapy in scarlet fever is to prevent acute rheumatic fever by initiating antibiotics within 9 days from the onset of symptoms. Penicillin is the drug of choice. Erythromycin can be used in patients allergic to penicillin. It is unclear if treatment can prevent the onset of post-streptococcal glomerulonephritis.

Treatment with doxycycline is the drug of choice in patients of any age for infection with *R rickettsia* and should be started as soon as RMSF is suspected.

Prognosis

The prognosis for most morbilliform rashes of childhood is generally good, with full resolution of symptoms unless children are very young, have congenital disease, have an underlying condition, or develop long-term complications. In some young infants, viruses that cause exanthems may produce severe complications such as pneumonia and encephalitis. Subacute sclerosing panencephalitis is a late-onset, rare, and serious degenerative CNS disease that occurs as a complication of wild-type measles infection. Some patients with roseola may develop chronic neurologic sequelae, but most cases are benign. The prognosis for Kawasaki disease is usually favorable with appropriate management. Up to 25% of untreated children and a fraction of those who have been treated may develop coronary artery aneurysms, sometimes with symptoms remaining silent for years, thus requiring vigilance during the acute phase. Kawasaki disease is the leading cause of acquired heart disease in children in the United States. In patients with severe infection with RMSF, long-term neurologic complications can be seen.

CASE RESOLUTION

The infant has the classic symptoms of measles. Normally, such a young infant would not yet have received immunization against measles because the first dose is administered at 12 to 15 months of age with the second dose at 4 to 6 years of age. Immunoglobulin will likely not modify the disease in this patient because her rash is nearly confluent, suggesting exposure more than 6 days ago. She should be evaluated for evidence of complications, including pneumonia. Unimmunized household contacts, as well as pregnant women and other contacts younger than 1 year, should receive Ig. Treatment is supportive.

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CHAPTER 140

Vesicular Exanthems

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CASE STUDY

A 2-year-old boy is evaluated for a 2-day history of fever (temperature: 39.5°C [103.1°F]), runny nose, decreased appetite, and a rash over the abdomen. He has had no previous known exposures to chickenpox (varicella) and no history of varicella vaccination. He attends child care daily. No one at home is ill. The boy is currently taking no medications except for acetaminophen for fever, and he has no history of dermatologic problems. On physical examination, his heart rate is 120 beats per minute, respiratory rate is 20 breaths per minute, and temperature is 38.0°C (100.4°F). The boy's overall appearance is nontoxic. The skin examination is significant for a few scattered erythematous vesicular lesions over the abdomen and 1 erythematous papule on the back. The rest of the examination is normal.

Questions

1. What are the most likely causes of vesicular exanthems in febrile children?
2. How can types of vesicular rashes be differentiated on the basis of patient history?
3. What are the key historical questions to ask?
4. What is the natural course of varicella?
5. What treatment options are available for children with varicella? How is the management different for immunocompromised children?
6. What options are available for vesicular exanthems other than chickenpox?

Exanthems are generalized, erythematous rashes with an underlying cause. They are most frequently caused by viral or bacterial infections. However, they can also be caused by noninfectious etiologies such as autoimmune disorders, drug reactions, genetic disorders, and physical injury. Infectious eruptions are most commonly morbilliform in the pediatric population, but they can present as vesicular, bullous, petechial, or purpuric eruptions. *Vesicles* are elevated, fluid-filled lesions that measure 1 cm or less (≤0.4 in) in diameter. Those that are larger than 1 cm (>0.4 in) are called *bullae*. *Vesicles* often lose their initial morphology quickly because they can break spontaneously or coalesce into bullae. They can arise de novo or from macules or papules. Vesicles may be discrete, grouped, generalized, or linear, depending on their etiology, and their specific distribution is often helpful in formulating a differential diagnosis.

History and Physical Examination

A thorough history should be obtained (Box 140.1). Health professionals must inquire about the patient's general health as well as the specific details of the eruption.

Although the physical examination focuses on the skin, other aspects of the examination are helpful diagnostically. Vital signs should be assessed to verify the presence or absence of fever. The oropharynx should be examined closely for any lesions on the tongue, gingiva, buccal mucosa, palate, anterior tonsillar pillars, and posterior pharynx. The lips should also be examined for any evidence of vesicular lesions that may occur with a primary or recurrent herpes simplex infection.

Patients should be completely unclothed to permit a thorough examination of the skin. The distribution of the lesions should be noted. Physicians should determine whether the vesicles are grouped in a particular dermatomal distribution, as with zoster (shingles), or more generally distributed and in various stages of development, as with varicella. A linear distribution may suggest contact with poison ivy or oak. Physicians should also note the following: Do the lesions include or exclude the palms and soles? Are the buttocks involved?

Box 140.1. What to Ask

Vesicular Exanthems

- How long has the child had the rash? Where is it located?
- Does the child have associated symptoms such as fever, runny nose, cough, or sore throat?
- Does the child have nonspecific symptoms, such as decreased appetite?
- If the child has any symptoms accompanying the rash, did these develop at the same time as the rash?
- What is the immunization status of the child?
- Is there any reason to suspect that the patient is relatively immunocompromised from chronic steroid use, chemotherapy, or an acquired immunodeficiency?
- Does the child have a history of similar lesions?
- Does anyone else in the family have a similar rash?
- Has the child been camping or hiking in the woods?
- Are there pregnant contacts?

Are the lesions concentrated on 1 specific part of the body, such as the feet and toes or the hands? Are the sizes of the lesions uniform? If not, are other larger bullous-like lesions present in addition to vesicles? It is also helpful, if at all possible, to examine the skin of family members for similar lesions.

Vesicular exanthems are eruptions of distinctive lesions that are raised and fluid filled (Box 140.2). They may be located anywhere on the child's body and, depending on the etiology, may or may not be pruritic. Other symptoms that may accompany such rashes include fever, upper respiratory symptoms, and gastrointestinal and central nervous system (CNS) involvement.

Epidemiology

Epidemiological factors can help differentiate infectious from noninfectious etiologies. Patient age, season of the year, presence or absence of similar cases in the community, and regular attendance at child care or school, which may contribute to exposure, should all be considered. Biological sex and ethnicity are usually less informative but can help distinguish certain diseases causing exanthems.

Primary varicella-zoster virus (human herpesvirus [HHV] 3), or chickenpox, is among the most common vesicular exanthems seen in childhood. Males and females are equally affected. Most reported cases in the pre-vaccine era were in children younger than 10 years. Since universal vaccination has been implemented, children aged 10 to 14 years are becoming the group with the greatest incidence of infection, although it is still less than during the pre-vaccine period. It is primarily transmitted person-to-person by airborne spread of aerosolized viral particles from vesicles of infected persons. It may also be transmitted through respiratory secretions and vertically from mother to fetus. It is extremely infectious, and transmission to susceptible household contacts is greater than 90%. The incubation period ranges from 10 to 21 days after exposure but can be longer (21–28 days) if varicella-zoster immune globulin is administered. Neonates born to mothers with active infection around the time of delivery can develop varicella 2 to 16 days after birth. Patients are considered contagious from 1 to 2 days before onset of cutaneous lesions until all are crusted over.

Human herpesvirus 1 and 2, also called herpes simplex virus (HSV), affect most adults worldwide. Historically, HHV-1 infections generally occurred outside the genital area and HHV-2 within the anogenital area. Now, either virus can be found in both areas. Neonatal infection is generally acquired at delivery from an infected mother who is often unaware of her infection. Human herpesvirus 1 is typically transmitted by direct contact with oral secretions or lesions and HHV-2 from direct contact with infected genital secretions. Shedding of viral particles can occur in the absence of active infection. The incubation for HHV infection beyond the neonatal period is 2 days to 2 weeks. Most affected neonates will have signs of clinical infection in the first postnatal month.

Hand-foot-and-mouth disease and herpangina are caused by enteroviral infections and occur worldwide. Outbreaks involving child care centers, schools, summer camps, hospital wards, military installations, communities, large geographic areas, and entire countries have been reported. They are transmitted person-to-person by the fecal-oral route. They also can be transmitted by contact with oral and respiratory secretions and, in the case of hand-foot-and-mouth disease, vesicle fluid. Most cases of these 2 conditions occur in infants and children. Hand-foot-and-mouth disease is most commonly caused by infection with coxsackievirus A16 or enterovirus 71 and is among the most recognizable viral exanthems in children and adults. The principal enterovirus serotypes associated with herpangina are coxsackieviruses A1 to A6, A8, A10, and A22. These enteroviral infections occur most commonly in summer and early fall. The usual incubation period for most enteroviruses is between 3 and 6 days.

Box 140.2. Diagnosis of Vesicular Exanthems in Pediatric Patients

- Raised, fluid-filled vesicles on the skin.
- Lesions may be pruritic.
- Possible associated fever, upper respiratory infection symptoms, myalgia.
- History of affected contacts.
- Lesions on mucous membranes.

Diagnosis and Differential Diagnoses

Primary Varicella-Zoster Virus (Chickenpox)

Primary varicella-zoster virus (chickenpox) infection usually consists of hundreds of vesicles, existing in various stages of resolution. Lesions progress from erythematous macules and papules to vesicles and, eventually, to pustules that then crust and heal normally without scarring unless secondarily infected and deeply inflamed. Characteristically, the vesicle has been described as a "dewdrop on a rose petal." Associated prodrome includes malaise and mild fever. Symptoms tend to be more severe in infants and older patients. Since universal vaccine implementation, breakthrough cases have become more common and have a milder clinical presentation. Fetal infection during the first or early second trimester can result in fetal demise or in congenital varicella syndrome, consisting of limb hypoplasia, cutaneous scarring, ophthalmic abnormalities, and CNS defects. Infection acquired from 5 days antepartum to 2 days postpartum can also be fatal because of the absence of protective maternal antibodies. Bullous varicella can result when *Staphylococcus aureus* infects the vesicles of chickenpox, with greater chance of scarring.

Modified varicella, also known as "breakthrough varicella," can occur in vaccinated people. Breakthrough varicella is usually milder than natural varicella, with less than 50 lesions, low or no fever, and shorter duration of rash. Most studies have noted breakthrough varicella occurring in fewer than 1% to 3% of vaccinated children

each year after vaccination. The rash may be atypical in appearance with fewer vesicles and predominance of maculopapular lesions. Breakthrough varicella is contagious, although less frequently transmitted than natural varicella.

Herpes zoster, a reactivation of a latent infection with varicella-zoster virus, can also cause a vesicular rash. The virus, which rests dormant in neuronal cells, travels along the nerves when reactivated and becomes released into the skin. It is generally a disease of older people, although children can be affected. In zoster, the lesions are grouped unilaterally in the distribution of 1 to 3 sensory dermatomes. It can be quite painful, and postherpetic neuralgia can last for months. In immunocompromised patients, the rash of zoster can become disseminated.

Human Herpesvirus 1 and 2 (Herpes Simplex Virus)

The onset of clinical illness of HSV-1 is usually sudden, with the appearance of multiple characteristic vesicular lesions superimposed on an inflammatory, erythematous base. Primary infection may also be associated with systemic symptoms, such as fever and malaise. The lesions can be painful and last for 10 to 14 days. Vesicles are usually grouped in a single anatomical site; however, autoinoculation of distant locations can occur. Although the symptoms can be severe, most primary HSV-1 infections are asymptomatic. Once HSV infection has occurred, the virus lives in a latent state in nerve cell bodies in ganglion neurons and can reactivate. The frequency and severity of reactivation is determined by many factors, including immunodeficiency or stress.

The clinical manifestations of primary genital HSV infection are highly variable. The initial presentation can be severe with painful genital ulcers, dysuria, fever, and tender local inguinal lymphadenopathy. In other patients, however, the infection is mild, subclinical, or entirely asymptomatic. There are no clear differences in clinical presentation based on infecting virus (ie, HSV-1 vs HSV-2).

Disseminated, CNS, or skin, eyes, and/or mouth HHV infection in an infant is usually caused by HHV-2, very severe, and often accompanied by skin findings. In children and adolescents, HHV-1 gingivostomatitis and perioral vesicles are the most common clinical findings and can also be asymptomatic. A prodrome of paresthesia with recurrent infection is not uncommon. There can also be an ulcerative enanthema. Human herpesvirus 1 and 2 persist for life in the sensory ganglia and, when reactivated, result in single or grouped vesicles, often on the vermilion border with an erythematous base. Triggers include stress, UV exposure, and fever.

Hand-foot-and-mouth Disease and Herpangina

Hand-foot-and-mouth disease is associated with a brief, mild prodrome of fever, malaise, and mouth pain. The exanthem consists of erythematous macules and papules with a central gray vesicle. Generally, the volar surfaces of the hands and feet, as well as the buttocks, tend to be involved. In a recent North American 2011–2012 epidemic, infection with coxsackievirus A6 resulted in hand-foot-and-mouth disease with more extensive areas of cutaneous involvement and more protean morphologies, as well as localization to areas of active dermatitis, termed "eczema coxsackium." The concomitant enanthema is seen on the tongue, buccal mucosa, palate, uvula, and anterior tonsillar pillars. In herpangina, patients acutely develop fever, malaise, headache, and neck pain. There is a painful enanthema of small grayish-white vesicles on the soft palate, uvula, buccal mucosa, pharynx, and tonsils. These ulcerate with a surrounding red halo.

Bullous Impetigo

Impetigo is the most common bacterial skin infection in children. Bullous impetigo is a less common form of impetigo than the non-bullous forms. Bullous impetigo is most frequently seen in the summer in warm, humid conditions and is easily spread among individuals in close contact. The infection may be classified as primary impetigo (direct bacterial invasion of previously normal skin) or secondary impetigo (superinfection at sites of minor skin trauma such as abrasions, minor trauma, and insect bites, or underlying conditions such as eczema) and is also sometimes referred to as impetiginization. There can be associated fever, weakness, and diarrhea, although there are often no systemic symptoms. Small vesicles enlarge rapidly into flaccid bullae that easily rupture. These lesions can be generalized and can arise from normal-appearing skin. The infection is usually caused by *S aureus,* phage group 2, and is a localized reaction to exfoliative toxin that causes loss of cell adhesion in the superficial epidermis by targeting the protein desmoglein 1. This condition affects mostly neonates, infants, and younger children.

Scabies

Scabies is transmitted during prolonged close contact with an infested individual. Scabies has an incubation period of 4 to 6 weeks in patients without previous exposure. Reexposed patients develop symptoms a few days after repeat exposure. Caused by the tiny mite *Sarcoptes scabiei,* it can cause an intensely pruritic, generally papular eruption, although vesicular lesions can occur. Commonly, secondary excoriations are seen (see Chapter 138). In older children and adults, interdigital folds, flexor wrists, waistline, trunk, and genital area are more commonly affected. A linear burrow is pathognomonic but often difficult to identify clinically. Patients younger than 2 years have involvement predominantly of the head, neck, palms, and soles. In this age group, the eruption is more likely to be vesicular. Arthropod bites can also result in isolated and scattered vesicles.

Fungal Pathogens

Fungal pathogens that cause tinea pedis include *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans,* and *Epidermophyton floccosum.* Infection can directly cause a scaly or vesicular rash or can result in a hypersensitivity reaction to the fungi, presenting as vesicles on the palms, soles, sides of the fingers, and, occasionally, on the extremities and trunk. *Trichophyton mentagrophytes* can cause vesicles and bullae on the medial foot. It can be associated with an id reaction, in which deep-seated pruritic

vesicles develop secondary to tinea infection elsewhere. An id reaction, most commonly on the hands, face, and trunk, can also result from tinea capitis, usually caused by *T tonsurans* and *Microsporum canis,* although it does not cause a vesicular exanthem on its own (see Chapter 136). The incubation periods of fungal infections are variable, and exact limits are unknown.

Pompholyx (Dyshidrotic Eczema)

Pompholyx (dyshidrotic eczema) is a disease that can occur in children with chronic eczematous dermatitis or atopic dermatitis but can occur in children who are nonatopic as well. The clinical appearance of pompholyx can be identical to that of an id reaction or fungal infection and consists of tapioca, pearl-like, deep-seated vesicles frequently seen on the palms and soles as well as the lateral sides of the fingers that are extremely pruritic. Secondary impetiginization (bacterial superinfection) is common. Cases can be acute and recurrent, as well as chronic.

Allergic Contact Dermatitis

A delayed type IV hypersensitivity reaction secondary to contact with plants of the genus *Toxicodendron* is a common cause of allergic contact dermatitis. The main allergen in these plants is a catechol. Rhus dermatitis is the prototypical allergic contact dermatitis, which develops about 1 to 3 days after exposure to plants such as poison ivy, oak, and sumac. Linear papules and vesicles are seen at points of contact between the plant antigen and the skin (see Chapter 138). Contact with other allergenic substances may also produce a vesicular rash, including nickel, rubber compounds, fragrances, and preservatives in cosmetics.

The differential diagnosis of acute vesicular exanthems can be organized according to the distribution of the lesions. Distinctive locations, as well as specific patterns, are important to consider in each individual case. The presence or absence of fever can assist in developing the appropriate differential diagnosis (Figure 140.1 and Box 140.3). Epidemiological as well as historical information may suggest the diagnosis. For example, known exposure to varicella-zoster virus (chickenpox) 10 to 21 days prior to a vesicular eruption facilitates diagnosis of this disease. A history of hiking, camping, or other outdoor activities suggests possible contact with poison ivy or oak. In addition, the presence of a specific prodrome can often be elicited with primary or recurrent herpes simplex. Pain on swallowing often occurs with enteroviral infection. A history of similar lesions lessens the likelihood of acute primary infection and suggests a chronic condition such as the recurrent disorder pompholyx.

Laboratory Tests

Typically few, if any, laboratory studies are necessary in healthy children with vesicular eruptions because the diagnosis is often made clinically. Clinical diagnosis is becoming more challenging because of fewer cases of varicella and milder, atypical cases in the vaccinated population. A Tzanck test of the base of a vesicle showing multinucleated giant cells may be useful in making a preliminary diagnosis of herpes simplex or varicella. Direct fluorescent antibody and polymerase chain reaction are rapid methods to diagnose varicella. Polymerase chain reaction can detect viral DNA from swabs of vesicles or scabs. This test is highly sensitive and widely available. Culture and polymerase chain reaction should be obtained for diagnosis of neonatal herpes simplex infection.

Definitive confirmation of scabies can be made by microscopic examination of skin scrapings from suspicious lesions. The presence of the adult mite or ova, larvae, nymphs, or feces (scybala) is diagnostic. For children with suspected tinea pedis, scale collected

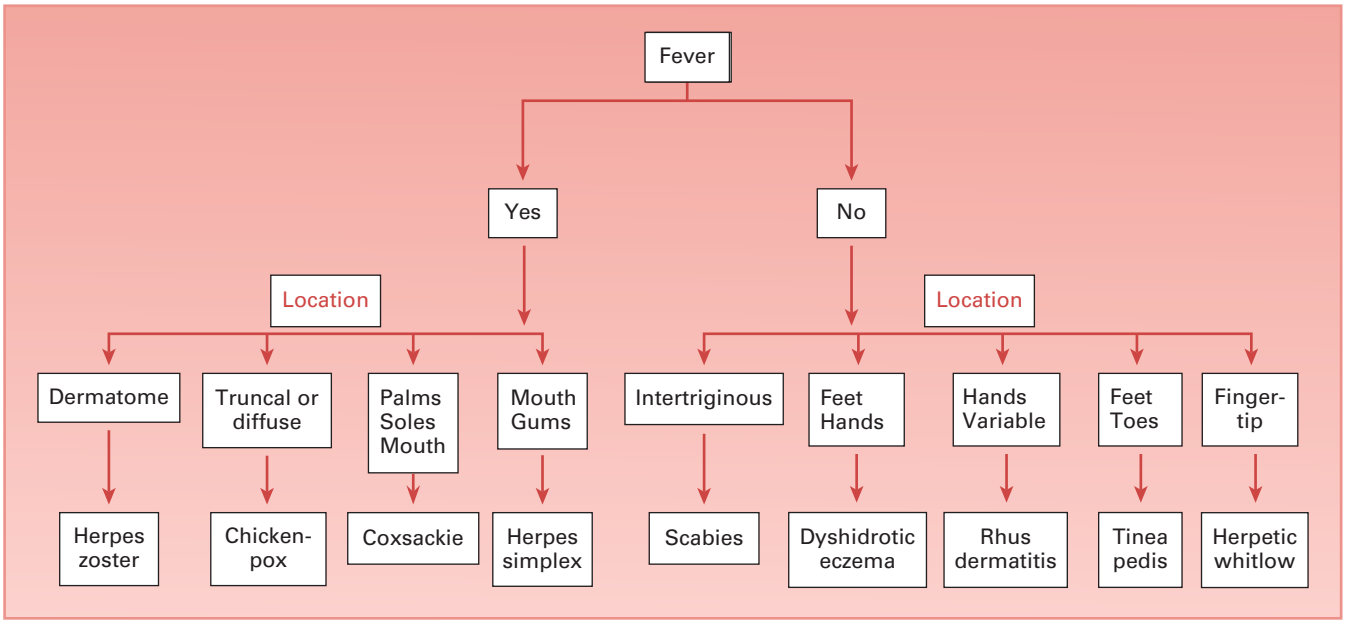

Figure 140.1. Approach to the evaluation of vesicular eruptions.

Box 140.3. Common Causes of Acute Vesicular Exanthems

Infectious

Viral

- Varicella-zoster
- Human herpesvirus 1 and 2
- Enterovirus

Bacterial

- *Staphylococcus aureus*

Fungal

- *Trichophyton rubrum*
- *Trichophyton mentagrophytes*
- *Trichophyton tonsurans*
- *Microsporum canis*
- *Epidermophyton floccosum*

Infestations

- Scabies (*Sarcoptes scabiei*)
- Arthropod bites

Noninfectious

- Allergic contact dermatitis
- Pompholyx (dyshidrotic eczema)
- Id reaction

from a skin scraping can be prepared with potassium hydroxide and examined under the microscope. Fungal cultures can also be obtained.

Pathophysiology

Vesicles and bullae arise from a cleavage at various levels of the skin within the epidermis (intraepidermal) or at the epidermal-dermal junction (subepidermal). Sometimes the 2 types of lesions can be differentiated based on the amount of pressure required to collapse the lesion, especially if the lesion is a large bulla. In addition, the thickness of the wall of a bulla can be estimated by its translucency or flaccidity. A biopsy of the lesion, however, is the only way to reliably differentiate between the 2 areas of separation, although this will not necessarily provide the diagnosis. Specific changes occur in the epidermis depending on the etiology of the vesicular exanthem. For example, with certain viral infections such as HHV, varicella, and herpes zoster, a hydropic (ballooning) degeneration of epidermal cells occurs.

In bullous impetigo, the vesicles and bullae are caused by staphylococcal exfoliative toxin that causes loss of cell adhesion in the superficial epidermis by targeting the protein desmoglein 1, which causes the keratinocytes in the granular layer of the epidermis to split apart. There are no bacteria seen within the blister cavity, and a few inflammatory cells can be present.

The rash caused by scabies infestation is the result of a hypersensitivity reaction to the proteins of the parasite. In vesicular lesions, there is spongiosis, or intercellular edema, in the epidermis caused by the mite, which can result in a vesicle. Spongiosis also leads to vesicle formation in pompholyx, although the pathogenesis of this disease is not known. Although pompholyx is also known as dyshidrotic eczema, "dyshidrotic" is a misnomer because this disease is not related to sweat gland dysfunction or occlusion. Spongiosis is also present in id reactions and allergic contact dermatitis.

Management

The mainstay of treatment for most vesicular eruptions is parent/guardian and child education as well as reassurance. For example, most varicella, herpes simplex, gingivostomatitis, hand-foot-and-mouth disease, and herpangina infections are self-limited and no treatment, except parental/guardian reassurance and education on adequate hydration, is necessary. These diseases can, however, be quite serious, as shown by the recent epidemic of enterovirus 71 in Asia, which resulted in death in severe cases. Any neonate with lesions suggestive of herpes simplex should also be worked up and treated aggressively because sequelae can be devastating. Depending on the etiology of the vesicular rash, children who are immunocompromised, such as those with HIV or AIDS, and patients who are undergoing treatment with chemotherapeutic agents or systemic corticosteroids may require specific intervention with the use of antiviral agents.

Topical agents such as calamine lotion and oatmeal baths should be used in children with intense pruritus or multiple lesions. Topical products, which are potentially sensitizing (eg, diphenhydramine-containing agents), should be used cautiously and discontinued if the condition is not improving. Cool, wet compresses with plain water or aluminum acetate (Burow solution) can be quite soothing in cases of rhus dermatitis, scabies, or tinea pedis.

Antipyretics (eg, acetaminophen) may be used to treat otherwise healthy children with varicella. Aspirin-containing medications should be avoided in children with varicella because of the association with Reye syndrome. Oral analgesics may also be indicated for symptomatic relief of pain associated with herpetic gingivostomatitis or enterovirus mouth lesions.

Oral antihistamines (ie, diphenhydramine or hydroxyzine) may be used in children with varicella or scabies for treatment of pruritus. These drugs are also helpful in treating pompholyx and rhus dermatitis. Although the sedating antihistamines are generally more effective, nonsedating antihistamines can also be used in the daytime, particularly for the more chronic pompholyx.

Steroids may be effective in the control of some vesicular rashes; however, the health professional must first be certain the lesions are not secondary to varicella or herpes simplex. In certain cases, steroids may be used in infectious diseases, such as eczema herpeticum, but in conjunction with antiviral therapy and under close monitoring. Topical steroids can be used for outbreaks of vesicles of pompholyx, as noted previously, reserving oral steroids for severe outbreaks. In severe cases of rhus dermatitis, a course of systemic steroids, such as prednisone, 1 to 2 mg/kg per day, may be warranted and generally requires at least 2 to 3 weeks of therapy. Topical steroids can also be used to treat an id reaction, as well as treating the underlying cause of the reaction. Use of an oral histamine-2 blocker, such as ranitidine or famotidine, can help prevent gastritis as a complication of oral prednisone.

Oral acyclovir or valacyclovir is not recommended routinely for the treatment of uncomplicated varicella in otherwise healthy children but should be considered when the risk of developing moderate to severe disease is increased. Acyclovir or valacyclovir is recommended in unvaccinated patients older than 12 years; those with chronic cutaneous or pulmonary disorders; those receiving chronic or short, intermittent courses of corticosteroids (systemic or aerosolized); or those receiving salicylates long-term. It can also be considered for secondary household infections and for those who may experience more severe disease. Intravenous (IV) acyclovir or oral valacyclovir, initiated within 24 hours of rash development, is recommended for patients who are immunocompromised. Oral acyclovir or valacyclovir may be warranted in pregnant women with varicella in their second or third trimester, with IV acyclovir for pregnant women with more serious complications. Acyclovir is most effective if initiated within the first 24 hours of the exanthem, although the effects on symptoms may be minimal. Varicella-zoster immune globulin may help modify the course of the disease.

An additional recommendation for children with varicella is to keep fingernails short to prevent superinfection of lesions from scratching. Children should drink plenty of fluids to avoid dehydration. Patients are considered contagious from 1 to 2 days prior to the onset of the rash until the lesions are all dried and crusted (usually 5–7 days after the rash develops), at which time they may return to school. In children with persistent or recurrent fever, secondary complications should be considered, such as bacterial superinfection with *S aureus* or group A beta-hemolytic *Streptococcus.* A rare association between primary varicella injection and invasive group A beta-hemolytic streptococcal infection resulting in streptococcal toxic shock syndrome and necrotizing fasciitis has been recognized.

Since 2006, the recommendation has been for 2 doses of varicella vaccine because immunity appears to wane with only 1 dose and sporadic outbreaks occur. Incidence of varicella infection has decreased significantly since this implementation, with 98% effectiveness with 2 doses versus 86% for 1 dose in a post-licensure study. Recipients of 2 doses are less likely to have breakthrough disease or zoster.

Intravenous acyclovir is the treatment of choice for neonates with herpes simplex infection. Primary genital infections should be treated with oral acyclovir or valacyclovir. Children with recurrent, frequent (>6 times a year) outbreaks of herpes simplex may benefit from suppressive therapy with 1 of these agents. *Herpetic whitlow* is a herpes simplex infection on the fingertip, usually as a result of direct autoinoculation from oral or genital lesions. Treatment is not required, although it may help with pain and faster healing. Herpes gladiatorum and "herpes rugbiaforum" are cutaneous herpes simplex infections on the skin of wrestlers and rugby players, respectively. While they do not require treatment with antiviral agents such as acyclovir, athletes should refrain from engaging in person-to-person contact when herpes lesions are present. *Eczema herpeticum* is a herpes simplex infection in children with underlying atopic dermatitis or other chronic skin disease that results in rapidly progressive widespread vesicles in areas of active underlying disease that then erode and crust. There can be significant fever and irritability, and severe infection may warrant hospitalization for treatment with IV acyclovir. Treatment with topical calcineurin inhibitors (eg, tacrolimus) is contraindicated.

Localized bullous impetigo in otherwise healthy patients can be treated with topical mupirocin 2% or retapamulin 1% ointments. Benefits of topical therapy include fewer side effects and lower risk for contributing to bacterial resistance compared with oral therapy. While over-the-counter triple antibiotic ointments (consisting of bacitracin-neomycin-polymyxin B) do have some activity against the organisms causing impetigo, they may not be as effective for treatment. Therefore, treatment of impetigo with these agents is not recommended. Bacitracin and neomycin can also cause contact dermatitis. More widespread or complicated infections require oral antistaphylococcal therapy with agents such as amoxicillin and clavulanate (Augmentin) or cephalexin (Keflex). Of note, children 8 years and younger should not be treated with doxycycline because of the potential for drug-induced tooth discoloration. Recurrent disease should warrant workup for carriage and treatment if needed. Local knowledge of methicillin-resistant *S aureus* rates and bacterial cultures should be considered.

In scabies, permethrin is recommended given its high efficacy and safety. However, topical sulfur is typically used for the treatment of infants younger than 2 months because of lack of regulatory approval for permethrin use in infants in this age group. Lindane should not be given to children younger than 10 years because of risk for systemic toxicity (see Chapter 138).

For the treatment of tinea pedis, topical antifungal agents in powder, cream, or ointment formulations can be effective when applied twice daily until clear. Discomfort can be alleviated with cool water or Burow solution soaks. Tinea pedis can be difficult to control. Its treatment is centered on meticulous foot hygiene. Because careful foot care is often not a priority for most patients, complete eradication is not realistic. Patients should be instructed to wash their feet and change their socks when they return from school, dry their feet completely, avoid occlusive shoes, and wear open-air shoes or sandals whenever possible. Topical antiperspirants may be needed (aluminum chloride). Cotton socks are recommended. In severe or refractory cases, an oral antifungal preparation such as griseofulvin, terbinafine hydrochloride, or itraconazole may be prescribed. Tinea capitis also requires oral antifungal therapy (see Chapter 136).

Prognosis

Overall, the prognosis for vesicular exanthems caused by infection is good, with most children recovering in 1 to 2 weeks, depending on the etiology. Secondary infections can occur with varicella, however, and should be suspected in children with persistent or recurrent fever. Additional complications in patients who are not immunosuppressed include bacterial superinfection of the skin, pneumonia, CNS involvement, Reye syndrome, glomerulonephritis, and arthritis. Complications from herpes simplex infections include conjunctivitis, keratitis, and encephalitis.

Secondary infections with skin flora can be a complication of any of these skin conditions because denuded lesions allow for superinfection. In addition, many of these rashes can be pruritic, resulting in open, excoriated skin.

CASE RESOLUTION

The toddler has a classic presentation of primary varicella (chickenpox). Management should include symptomatic treatment with acetaminophen and antihistamines, along with topical preparations such as calamine lotion and oatmeal baths. The parents should be instructed on the natural course of this infection and be informed that the infection is highly contagious. In addition, symptoms indicating possible complications, such as persistent or recurrent fever, tenderness, warmth, redness or swelling of the skin, leaking pus, and shortness of breath, should be reviewed with the parents.

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PART 14

Social Determinants of Health

CHAPTER 141

Social Determinants of Health: Principles

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CASE STUDY

John is a 12-year-old boy who is at your clinic for a sports physical. He is with his older sister because his mother is working and could not bring him in for the visit. He has 3 younger siblings at home. John says he is getting "mostly Cs" in school. When asked why he might be struggling in school, he responds by saying, "I'm trying my best." He plans on playing football this fall and is excited about the possibility of a "scholarship someday." His older sister remarks, "You can't be getting to school late if you want to get good grades."

Questions

1. What is the value of information about a patient's school and school performance? What is the best approach to learning about a patient's school performance?
2. How would you solicit information about a family's nonmedical needs and concerns?
3. What is the relevance of information about a family's structure and resources?
4. What role can a pediatrician play in assisting a family's access to necessary resources?

Children are born, live, grow, develop, and learn within an ecosystem that determines and influences their health, well-being, and overall life course; the factors comprising this ecosystem are known as the *social determinants of health* (SDoH). These factors are rooted in history, institutions, communities, and culture but are continually shaped by changes in the surrounding socioeconomic environment. The SDoH exist either in concert with health and well-being (ie, strengths or assets) or in opposition to health and well-being (ie, risks or needs). The combination of risks and strengths are not static; rather, they act in a dynamic fashion to uniquely shape and influence a child's life at any given time.

The SDoH have been conceptualized and categorized in myriad ways. The World Health Organization Commission on Social Determinants of Health formulated a comprehensive framework that conceptualizes the intersections of and relationships between the structural and intermediary determinants that affect health and well-being (Figure 141.1). This construct highlights the dynamic connections between the factors at play in patients' lives. On a national level in the United States, the public health initiative Healthy People 2020 has distilled the large constellation of the SDoH into overarching themes identified by 5 key domains that provide for actionable areas of focus: neighborhood and built environment, social and community context, health and health care, education, and economic stability (Figure 141.2).

The duality of individuals existing within the broader context of a population is an important point for the physician to consider. At a population level, it has been proposed that social factors and the social ecosystem account for more than one-half of the influence on health (Figure 141.3). The other significant contributors are health behaviors and medical care. In sharp contrast, the contribution of genes and biology are rather small. At the individual level, these findings underscore the immense importance and influence of social determinants on individual health.

The recognition that the health of individuals and populations hinges on much more than the underpinnings of physiology is of central importance to understanding the role of health professionals in the larger context of patients' lives. In fact, as SDoH themselves, health professionals play an integral role as mediators of other influential factors in their patients' lives. In the role of mediator, the individual physician has the ability to support favorable situations and mitigate adverse conditions and consequences in the lives of that physician's patients.

Pediatricians in particular have the unique potential to optimize the healthy development and life-course trajectory of the children and adolescents under their care. This presents both a challenge and an opportunity to recognize and address the SDoH that influence the lives of individual patients, the population served in the clinical setting, and the community in which the pediatrician practices.

Role of the Pediatrician

From its inception, the specialty of pediatrics has had a rich tradition of recognizing and working to ameliorate SDoH. As witnesses to the effect of social, political, and economic policies on children, pediatricians have expertise that necessarily extends beyond the diagnosis and management of disease. The combination

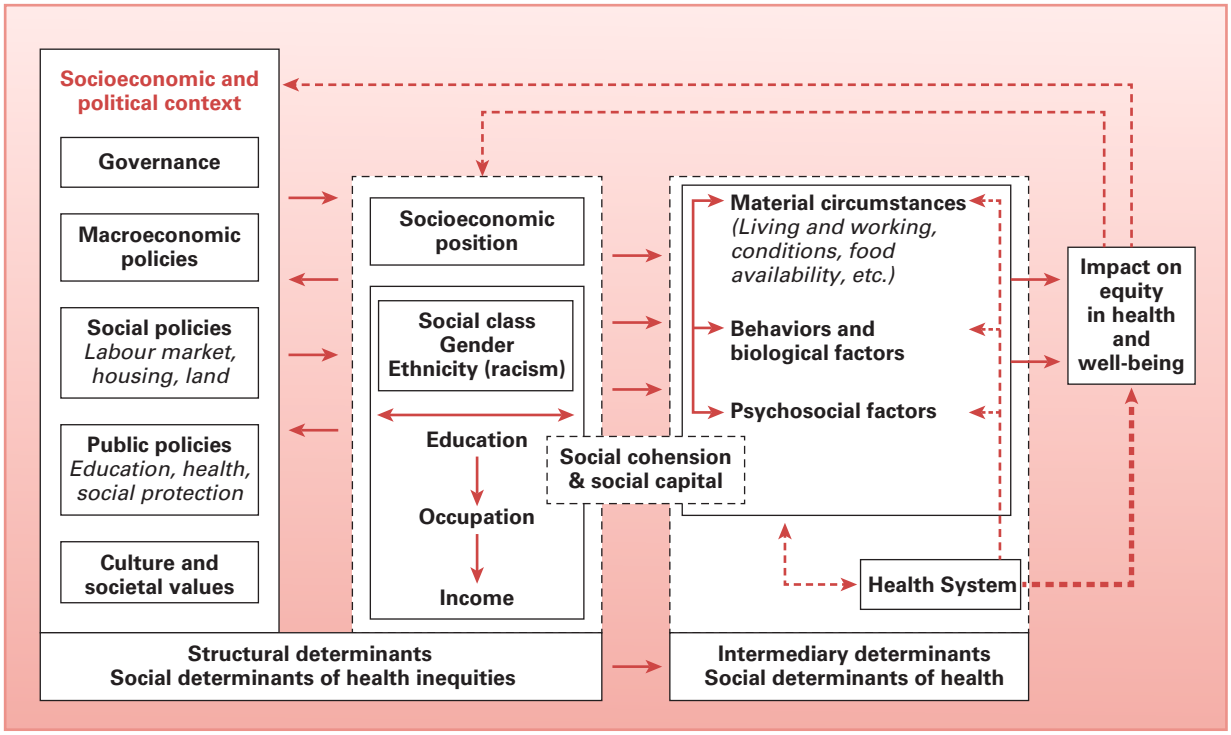

Figure 141.1. World Health Organization Commission on Social Determinants of Health conceptual framework for social determinants of health.
Reprinted with permission from Solar O, Irwin A. *A Conceptual Framework for Action on the Social Determinants of Health: Health Discussion Paper 2 (Policy and Practice).* Geneva, Switzerland: World Health Organization; 2010. http://apps.who.int/iris/bitstream/10665/44489/1/9789241500852_eng.pdf.

of pediatricians' expertise of the growth and development of children as well as their status as trusted voices and advisors in society on behalf of children allows pediatricians to serve as both advocates for children and active agents of change in children's lives. In practice, however, balancing the demands of providing medical care with the task of recognizing, assessing, and addressing the circumstances that can hinder or optimize the health and well-being of children is challenging. However, an organized process is available that can and should be applied to address SDoH. Moreover, the thoughtful approach and concerted effort required of pediatricians concerning these circumstances is not unlike that applied to identifying, assessing, diagnosing, and managing medical conditions. Similar to the traditional clinical approach to care, this process is characterized by actionable items, including screening, triage, identification, assessment, and intervention or referral. Most important, the skills and tools involved in this process also serve to augment and complement medical care, with the shared benefits of improving physical and mental health and promoting healthy growth and development.

Screening for Needs

Various screening procedures, tools, and questionnaires are commonly used in pediatrics. Most medical visits involve a patient intake process, which usually includes the use of questionnaires, triage, and assessment of vital signs. The primary reason for presentation is assessed, and measurements such as weight, height, temperature, and blood pressure are recorded. Similarly, well-child and health supervision visits usually include targeted age-based screening and assessment of developmental milestones. Additionally, new patients or patients who have not been seen recently often are asked to report on known health conditions and recent changes in health status. Patients and families are less commonly screened for the components and domains of the SDoH.

As a result of recommendations from the American Academy of Pediatrics and other trusted sources, however, screening for mental health symptoms, psychosocial stressors, and food insecurity have recently become more commonplace in some practice settings. Dedicated screening for the social determinants particular to any given patient should be included as part of usual protocol for all patients. Such screening is akin to obtaining vital signs in that it allows the physician to identify risks to health that may be as important to well-being as height or weight, if not more so. For example, knowing from height and weight measurements that a child has obesity is less beneficial than also knowing that the child has a parent who is unemployed and whose family is experiencing food insecurity. The information drawn from both screenings is of vital importance both during the clinical encounter and in the approach to management.

Screening requires a balanced approach involving integration of the clinical workflow, existing and emerging needs in the community, and knowledge of available resources. Furthermore, relying on clinical judgment alone for the existence of SDoH needs or risks in each family is problematic. Like the ability of pediatricians to recognize anemia, obesity, maternal depression, and developmental risk, pediatricians may recognize risk factors for negative SDoH in a patient's history, but identification of opportunities to support families requires a systematic approach and goes beyond recognition. Negative SDoH are often stigmatizing and linked to a family's past trauma, and as a result a family may be less likely to volunteer any needs to the pediatrician. This requires

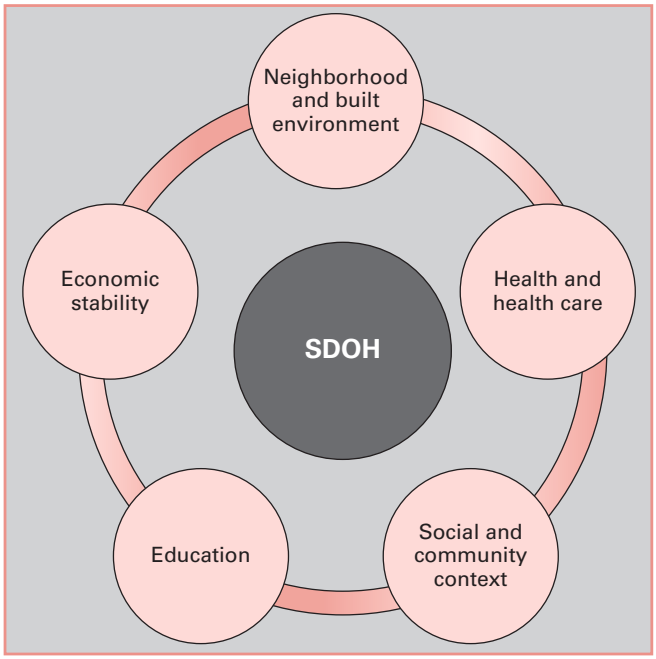

Figure 141.2. Healthy People 2020 focus areas for social determinants of health (SDOH) in the United States.

Reprinted from Office of Disease Prevention and Health Promotion. Social determinants of health. HealthyPeople.gov website. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health.

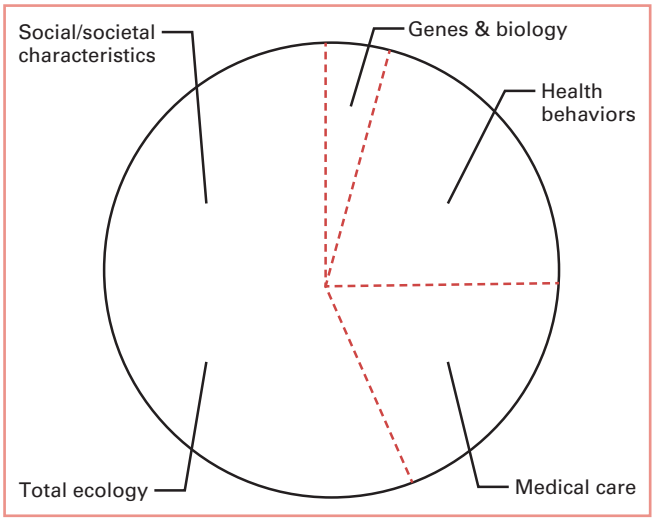

Figure 141.3. Determinants of population health. The dashed lines convey estimates of the various influences. The absence of a line separating total ecology from social/societal characteristics reflects the lack of quantitative knowledge at this time.

Reprinted with permission from Tarlov AR. Public policy frameworks for improving population health. *Ann N Y Acad Sci*. 1999;896(1):281–293.

health professionals to rely on their own unconscious biases along with their clinical experience to judge which families may have additional needs in an already busy, short encounter and can lead to over-detection or under-detection of SDoH risks and strengths.

Screening for SDoH affords pediatricians the opportunity to affect long-lasting change in patients' lives, but effecting meaningful change requires purposeful preparation. Understanding the needs and assets of the population and community served in a given clinical setting is essential. To begin this process, a needs assessment is conducted to understand what needs are most prevalent in the community served. The information gathered through the needs assessment is paired with an asset map to help the physician and staff match identified needs to available resources. This pairing is important to ensure that a physician does not develop a screening protocol that will identify risks that cannot be addressed using existing local resources. This process provides an opportunity to leverage knowledge of community stakeholders (Box 141.1) to augment information gleaned in the needs assessment. In the clinic with limited time and resources for undertaking a formal needs assessment and creating an asset map, the knowledge and experience of key stakeholders with positive relationships with the community can be leveraged to increase feasibility.

Many validated tools exist to screen for SDoH needs, but no standard tool has yet been identified. Few tools exist to assess SDoH assets. Single-domain screening tools (eg, the 2-item Food Insecurity Screener) focus on 1 specific domain, whereas comprehensive screening tools (eg, the 12-item Well Child Care, Evaluation, Community Resources, Advocacy, Referral, Education [WE CARE]) focus on multiple domains of risk. In this ever-evolving landscape, many practices choose questions from validated screening tools to create their own tailored screening tools based on their own needs assessment and local asset map. Screening modality, whether verbal, paper, or electronic, is also tailored to the workflow of each clinical setting. Personnel performing the screening usually depend on the screening modality. For example, in clinical settings in which families complete previsit questionnaires electronically, SDoH screening may be performed as part of that questionnaire, but in settings in which other screenings are paper based and delivered by ancillary staff, SDoH screening may be included with those other paper-based workflows.

Most SDoH needs are not identifiable via growth parameters, laboratory studies, or physical examination; thus, specific screening for SDoH has been recommended as part of routine well-child care. Additional consideration should be given to SDoH related to the disease process or the presenting symptom, or as otherwise indicated. Food insecurity screening at follow-up visits for obesity and weight checks for failure to thrive are excellent examples of situations in which additional consideration should be given to SDoH. Likewise, standard questions about habitability and smoking at an asthma visit might be enhanced by asking additional questions about financial needs and resulting parental stress should the parent mention the recent loss of a job. In the clinical setting in which formal screening is not conducted or in which a validated screening tool or individual to perform such a screening are not available, the physician can use the IHELLP (income, habitability, education, legal status, literacy, personal safety) mnemonic to guide discussions with families to identify needs.

Although each clinical setting and family situation is unique, certain best practices can be followed when performing SDoH screening. *Universal screening*, or screening all families, decreases the likelihood that implicit bias will negatively affect screening and increases sensitivity of the instrument. *Screening for risks and strengths* identifies assets of which families may not have been aware, and these assets can be used to counterbalance challenges the family is experiencing and build parental confidence and self-efficacy. To elicit strengths, the physician can either engage the family in

Box 141.1. Social Determinants of Health: Risks and Strengths

Risks

- Educational attainment
- Poverty
- Bullying
- Immigration status
- Intimate partner violence
- Neighborhood violence
- Social/economic stress
- Parental mental health
- Social disruption
- Family structure
- Parental obligations/time constraints
- Lack of financial or social resources
- Lack of knowledge about services (eg, social support, educational)
- Immigration status

Strengths

- Family/community connectedness (ie, social capital)
  - — Growth mindset
  - — Education
  - — Family structure (ie, supportive, caring adults to nurture child)
  - — Resiliency
  - — Family role models
  - — Safe neighborhoods
  - — Safe, high-quality schools
  - — Stable and habitable housing
  - — Access to nutritious food
  - — Access to job opportunities
  - — Access to reliable transportation
  - — Access to medical care, including behavioral health and wellness care
  - — Social customs, practices, norms
- Strengthening Families Protective Factors[a]
  - — Parental resilience
  - — Concrete supports
  - — Social connections
  - — Knowledge of parenting and child development
  - — Social and emotional competence of children
- Centers for Disease Control and Prevention protective factors[b]
  - — Nurturing
  - — Stability
  - — Safety

Resources

- Government services
  - — Supplemental Nutrition Assistance Program (SNAP)
  - — Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)
  - — Temporary Assistance for Needy Families (TANF)
  - — Earned-Income Tax Credit (EITC)
- Community agencies
  - — Anti-poverty agencies
  - — Specific advocacy agencies (eg, intimate partner violence)
  - — Food banks
- Early childhood systems
  - — Parenting supports
  - — Developmental supports (eg, Early Head Start, Head Start)
  - — Home visiting
- Social/civic groups
  - — United Way, YMCA
  - — Churches/Religious institutions
- Medical-legal partnerships

[a] Center for the Study of Social Policy. Strengthening families. CSSP.org website. https://cssp.org/our-work/project/strengthening-families.

[b] National Center for Injury Prevention and Control. Children Benefit When Parents Have Safe, Stable, Nurturing Relationships. Atlanta, GA: Centers for Disease Control and Prevention. https://www.cdc.gov/violenceprevention/pdf/SSNRs-for-Parents.pdf.

problem solving for a particular risk to help them identify their strengths or highlight strengths noted during the clinical encounter. Screening tools should be linguistically appropriate with attention to literacy level such that respondents with limited English proficiency or low literacy in any language can use them. If screening is delivered verbally, interpreters should be used to communicate with families with limited English proficiency. Because families may feel shame, guilt, or frustration about having SDoH needs or fear being reported as neglectful if they disclose needs, the physician should pose clear questions and remain nonjudgmental.

Principles of trauma-informed care should be used with screening because SDoH needs are often linked to past traumas, both individual and societal. For these families, disclosing needs is usually not risk free, whether the risk is the real risk of deportation or the theoretical risk of being reported as neglectful for having food insecurity and requiring support to meet the family's nutritional needs. Because many families are not accustomed to answering SDoH questions in clinical care, families should be presented with a clear rationale for screening and expected results. For written and electronic screening tools, a simple statement included on the tool itself is recommended. Screening should also be culturally and structurally competent, acknowledging that in the ever-changing lives of families, structural and intermediary social determinants work together to affect health equity (Figure 141.3). Recognition and acknowledgement of the current socioeconomic and political contexts as well as some understanding of the historical context for why inequities exist, is imperative. Purposeful acknowledgement of what cannot be addressed by the family alone because of the effects of certain systemic societal factors validates a family's experience.

Screening effectively without providing meaningful intervention does little to improve a family's outcomes. After screening to determine existing needs and assets, the physician must confirm what help the family desires to facilitate appropriate intervention. The role of appropriate universal and targeted screening cannot be overstated. It is the essential first

step in a complete and comprehensive assessment that will inform and guide management.

Comprehensive Assessment

In addition to screening, a comprehensive assessment and understanding of the unique factors present in each patient's life is incomplete without a robust family and social history. Medical students are often taught the maxim that a thorough history is indispensable and the key to most diagnoses. In practice, however, elements of a full and complete history may be overlooked or underappreciated. As indicated by presenting symptoms, screening, or known needs, the physician must aim to broaden the traditional cursory family and social history to fully account for the dynamic between medical, social, and family factors.

The family history must be inclusive of queries concerning family structure, paying particular attention to relationships and the roles of each caregiver in a patient's life, as well as where a child routinely spends time. Using this approach both elucidates a family's social context and helps the physician identify family preferences and practices.

While taking this history, it is important for the physician to be aware of and acknowledge the physician's own unconscious and conscious biases to avoid either imposing the norms of the examiner onto the family or inadvertently judging a family for not assimilating to the norms of the culture to which the examiner ascribes. For example, a biased view may incorrectly judge a family with 2 generations living in the same home as indicative of economic strain, rather than the preferred choice and practice for the family. Conversely, a child with a large number of caregivers with concomitant family dysfunction may be cause for chaos and may constitute a negative social determinant, whereas another child with stable family relationships will simply have more care and affection from a larger group of caregivers. The physician must appropriately and respectfully probe to fully understand the context of the history obtained.

A dedicated family and social history is also essential to explore relevant connections to medical conditions and findings. Special attention should be paid to common reports in children, because often presentations are not straightforward. For example, "belly pain" or "headache" may be a somatic manifestation of underlying psychosocial stress or strain. Such attention is particularly important in identifying mental health needs. Similarly, a seemingly stable family structure may belie underlying tensions and concerns, such as the well-adjusted family that may otherwise be coping with neighborhood safety concerns or immigration needs. Conversely, simple questions, such as, "What are your plans for the summer?" could uncover an unknown potential benefit from additional resources, such as educational enrichment summer programs offered by the local municipality.

Finally, a comprehensive assessment of the intersection of social and medical needs is of utmost importance when managing co-occurring social and medical complexity. Consider the case of a child with cerebral palsy who has previously exhibited failure to thrive and presents for follow-up after a recent admission for pneumonia. The physician should revisit elements from the family and social history that may be relevant to either the recent admission or future management at home, paying careful attention to possible changes in the child's environment, such as schooling, caregivers, housing conditions, and employment. A change may have occurred in medical attention at school or in insurance coverage for a necessary medication. Even seemingly trivial details, such as installation of new flooring in a home or a new family pet, may have relevance for their role in exacerbating underlying allergies. Any and all details are helpful in building a detailed history for use in making a complete assessment.

No substitute exists for a thorough and conscientious approach to history taking. The guiding force in this endeavor is a desire to become as intimately acquainted as possible with the conditions present in the lives of the patient and family. The physician must strike a balance between obtaining new information and confirming past information, with the aim of building a strong patient relationship or exploring a focused need. Most important, comprehensive history taking requires thoughtful weighing of the relevance of both positive and negative findings to each patient in light of individual screening, known or preventable conditions, possible complications, and potential benefits. The goal of the physician should be to make a comprehensive and unbiased assessment of the risks and strengths present for every child and family.

Differential Diagnosis of Risks and Strengths

Social determinants of health often have a negative connotation as consisting solely of risks, when in reality, every family has both risks and strengths that lie along a continuum rather than absolute positives or negatives. Approaching and narrowing a SDoH differential is unique in that the family—not the physician—is the expert in its own lived experience. Framing an approach to SDoH in terms of risks and strengths, in collaboration with a family, can help prioritize interventions as well as activate and empower the family.

Although identifying risks from screening tools and a history is relatively straightforward, elucidating a full differential that incorporates the interconnectedness of risks, strengths, and resources requires additional consideration (Box 141.1). Risks can be categorized based on Maslow's hierarchy of needs (Figure 141.4). Thoughtful specific attention to each level of this hierarchy (physiologic, safety, belonging, esteem and respect, achieving potential) helps to identify and address many of a family's vulnerabilities, and is especially important given children's particular susceptibility to the effects of their environment. Social and physical risks tend to be cumulative. Further clarifying the context of these risks directly with the family provides insight into stressors and life events that may have preceded or precipitated risks and helps the physician determine whether these risks are transient or fixed.

Unlike risks, SDoH strengths typically are gleaned from the history rather than specific screening tools. Narrowing the differential can be performed by general problem solving or problem solving around a particular risk with the family, such as specifically asking, "Who do you reach out to when you need help?" or "How can we go about helping with this today?" Such questions clearly signal

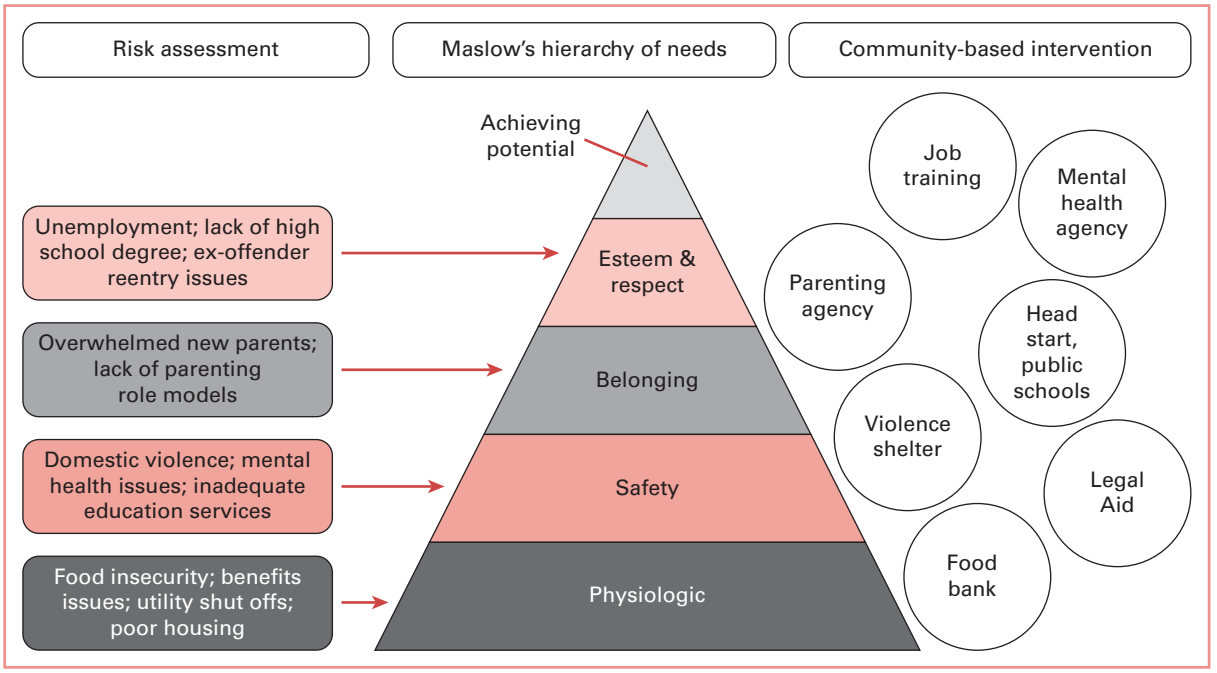

Figure 141.4. Conceptual road map that links risk assessment to community-based interventions using Maslow's Hierarchy of Needs.
Reprinted with permission from Henize AW, Beck AF, Klein MD, Adams M, Kahn RS. A road map to address the social determinants of health through community collaboration. *Pediatrics*. 2015;136(4):e993-e1001.

that the pediatrician and family are members of a team working to solve this problem for the child, and such an approach often helps the family identify strengths they had not considered.

Two commonly used frameworks delineate the domains of strengths. The first is the Strengthening Families Protective Factors Framework, which has 5 protective factors: (1) parental resilience (ability to problem solve when presented with challenges and know when to ask for help); (2) social connection (network of support that includes family, friends, and community supports); (3) concrete supports in time of need (basic needs, such as food and shelter); (4) knowledge of parenting and child development (understanding what to expect for a child's behavior based on age); and (5) social and emotional competence of children (a child's ability to self-regulate and communicate needs and feelings in a developmentally appropriate manner).

The second framework is the Centers for Disease Control and Prevention (CDC) protective factors of nurturing, stability, and safety. These include access to nutritious food, job opportunities with transportation to get to them, and medical care encompassing behavioral health and wellness care. Safety specifically highlights neighborhood and school safety, and stability highlights stable and habitable housing. The Protective Factors Framework provides a relational approach, whereas the CDC protective factors provide an approach that can easily mirror specific domains of SDoH risk.

Documenting the risks and strengths of a particular family at a particular point in time runs the risk of conceptualizing these needs and assets as static, which rarely is the case. Using the 3 As of assess, agree, and address scaffolds an approach that takes this into account. Assess involves using the comprehensive evaluation (ie, screenings and a full social history) to guide the physician's next steps. Agree involves the physician using the teach-back method to summarize what was learned in the interview and probing further to clarify strengths and risks. Additionally, proactively engaging the family in problem solving identifies shared targets and a plan for what the family finds most pressing. It also provides space for negotiation and clarification when the physician's concerns may differ considerably from those of the family, thereby allowing the family to use its strengths to temporize the situation until the family is ready to address its next prioritized concern. Finally, the pediatrician and family can discuss treatment options to address the family's prioritized risks and strengths.

Management: Providing Targeted Resources and Support

The role of the pediatrician in managing the SDoH consists of providing targeted resources and support. The most essential needs of the patient exist beyond the walls of the clinic, and the physician can provide a necessary link between needs and resources. Children are seen in outpatient pediatric care at least 10 times in the first 2 years after birth; thus, pediatricians are uniquely positioned to affect children's lives. Even with this number of contacts, the SDoH risks and strengths children encounter outweigh the influence of these health care encounters and cannot be fully addressed through clinical care alone. Therefore, at each office visit it is necessary to highlight strengths while identifying and addressing potential risks to health. Similar to engaging collaborative management with medical subspecialists when specialty care is required, often the physician must refer to other professionals and partners in the community with the necessary expertise and resources. A useful approach is providing targeted resources for identified needs in accordance with Maslow's hierarchy of needs (Figure 141.4). It is equally important for the physician to recognize, highlight, and support strengths

as well as promote self-efficacy at each office visit. In managing SDoH, the pediatrician embarks on an iterative process with each patient and family in which each follow-up visit serves as an opportunity for further advocacy and problem solving with families as well as an opportunity to highlight even the smallest successes as concrete examples of self-efficacy on which to build the family's strengths, confidence, and agency. Ultimately, the physician must take a family-centered approach imbued with shared decision making to develop an adaptive and evolving individualized care plan to optimize the healthy trajectory of each child.

CASE RESOLUTION

A thorough social and family history reveals that John's mother is a single parent working 2 jobs and that although John has some free time after school, often he is tasked with helping his older sister take care of his younger siblings when his mother is working the night shift. Screening for social needs identifies that his older sister reports that their family is coping with an overcrowded living situation and recently increased cost of rent. A dedicated psychosocial history and screening reveals that John has been having increasing difficulty with math assignments. He also often feels generally anxious and worried, but more so before tests. He is able to confide in his older sister, whom he considers a confidant and advisor. Further probing reveals that John is happiest when he is with his whole family, including his older sister, his mother, and all siblings. Although she is not a parent, John's sister is most concerned with how she can help John be more successful in school. Although they both wish they had more room in the home, John and his sister are proud of their unique contributions to help their family and the way in which they help each other. In addressing the housing insecurity, you refer the family to a local community housing support agency. You arrange for John to be seen by a behavioral counselor for cognitive therapy for his anxiety. You also share a handout for an after-school educational and tutoring program run by the local parks and recreation department, which John and his siblings can attend and still have family time in the evening. Finally, your office staff forwards a letter to the school system to initiate an evaluation for an Individualized Education Program (IEP). You schedule a follow-up visit to reassess John's anxiety and the status of the IEP as well as to confirm connection to the housing agency and after-school program.

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CHAPTER 142

Adverse Childhood Experiences: Trauma-Informed Care

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CASE STUDY

Chris is an 11-year-old boy presenting to your clinic for concerns about frequent bedwetting. He is accompanied to the visit by his stepfather. His parents are divorced, and his biological father is currently in jail for domestic violence. His biological father has a history of alcohol use and attention-deficit/hyperactivity disorder. His mother has a history of depression. Chris shares that he is embarrassed by his almost nightly bedwetting, and his stepfather adds that Chris has never been dry at night. His stepfather further mentions that Chris was recently suspended from school for 1 day for hitting another child. When the stepfather went to pick up Chris that day, the teacher stated Chris was having difficulty focusing in class and that his reading skills were below grade level. Chris commented, "Yeah, I hit him. He took some of my lunch and I really got mad."

Questions

1. What is an Adverse Childhood Experiences score, and how is it calculated?
2. What presenting symptoms might trigger adverse childhood experiences screening? What questions should you ask the family or patient to help determine the cause of unexplained symptoms?
3. How would you determine Chris's score? How does this score affect his risk for chronic disease?
4. What is meant by "Pair of ACEs"?
5. What is meant by protective/resilience factors? Can you identify any for Chris in the case study?

Children require safe, stable, nurturing relationships at home and in their community to promote optimal health and well-being throughout the life span. Children's responsive relationships with caregivers build healthy brain architecture and wiring over time. Adverse childhood experiences (ACEs) during the first 18 years after birth include exposure to abuse, neglect, and household dysfunction; disrupt healthy development; and can have a negative effect on adult mental and physical health and functioning. The ACE score is a determination of the number of ACEs to which a patient has been exposed. This score is based on the types of trauma included in the 3 categories of ACEs (ie, abuse, neglect, household dysfunction) (Box 142.1). Each individual ACE type counts for 1 point. The lowest score achievable is zero (no ACEs) and the highest is 10 (every ACE type). A child who has been exposed to emotional abuse and parental divorce, for example, is assigned an ACE score of 2.

The detrimental effects of these ACEs include adoption of unhealthy behavioral coping strategies, increased risk of chronic disease in adulthood, and difficulty with interpersonal relationships and work performance (Box 142.2). A dose-response relationship is observed, with exposure to more ACEs being associated with increased risk for more adverse outcomes later in life. Experience of 6 or more of these ACEs can result in up to a 20-year reduction in life span. Exposure to ACEs can affect the next generation as well, with the children of parents who experienced childhood adversity being at increased risk for developmental delays and health-harming behaviors.

Box 142.1. Categories of Adverse Childhood Experiences (ACEs) Used in Calculating the ACE Score

Abuse

- Emotional
- Physical
- Sexual

Neglect

- Emotional
- Physical

Household Dysfunction

- Domestic violence
- Incarcerated household member
- Mental illness
- Parental separation or divorce
- Substance and/or alcohol abuse

Box 142.2. Adverse Effects of Adverse Childhood Experiences Over the Life Span

Unhealthy Coping Strategies

- Alcohol and/or drug use, including intravenous drug use
- Multiple sexual partners
- Sedentary lifestyle or obesity
- Smoking

Health Effects

- Autoimmune disease
- Cancer
- Chronic pulmonary disease
- Diabetes
- Ischemic heart disease
- Liver disease
- Stroke

Mental Health Effects

- Depression
- Suicide attempt(s)

Lifestyle Effects

- Missed work
- Poor academic achievement
- Poor health quality of life
- Risk of intimate partner violence

More recently, other forms of adversity experienced in the environments in which children live, learn, and play (eg, poverty, racism, bullying, community violence) have been recognized as having similar negative effects on lifetime health. These environmental conditions in which children are born, grow, live, work, and age are referred to as the *social determinants of health* (see Chapter 141). According to the World Health Organization, the social determinants of health are responsible for most health inequities, that is, "the unfair and avoidable difference in health status seen within and between countries." In the United States, the wealthiest segment of the population has a 10- to 15-year longer life span than the poorest segment, an outcome that is related to differences in health-related behaviors, chronic disease, and injury. Together, ACEs and adverse community environments comprise the "Pair of ACEs" (Figure 142.1).

The Pair of ACEs tree illustrates how adversity within the family and adversity in the community together negatively affect children. Adverse childhood experiences exert their deleterious effect on health through excessive activation of the body's stress response on the developing brain and body. A child adapts to the negative home and world experiences the child encounters at the expense of longer term health. Positive supportive experiences at home and in the community can buffer and mitigate the effects, however. Because of the pervasive nature and long-lasting consequences of childhood adversity, addressing its roots and effects is an urgent public health concern.

Epidemiology

The original Adverse Childhood Experiences (ACE) Study published in 1998, based on information from more than 17,000 middle-class Americans, documented clearly that childhood adversity contributes significantly to negative adult physical and mental health outcomes. Sixty-four percent of adults recalled having at least 1 ACE, with 12% reporting 4 or more ACEs. Subsequent surveys have confirmed similar results in many states and many countries. Exposure to ACEs cuts across all strata of society. However, exposure to a higher number of ACEs disproportionately affects adults identifying as low income, low education, multiracial, or bisexual. The most common ACEs recalled by adults were emotional abuse, parental separation or divorce, and household substance abuse. Several ACEs tend to co-occur and can have intergenerational effects.

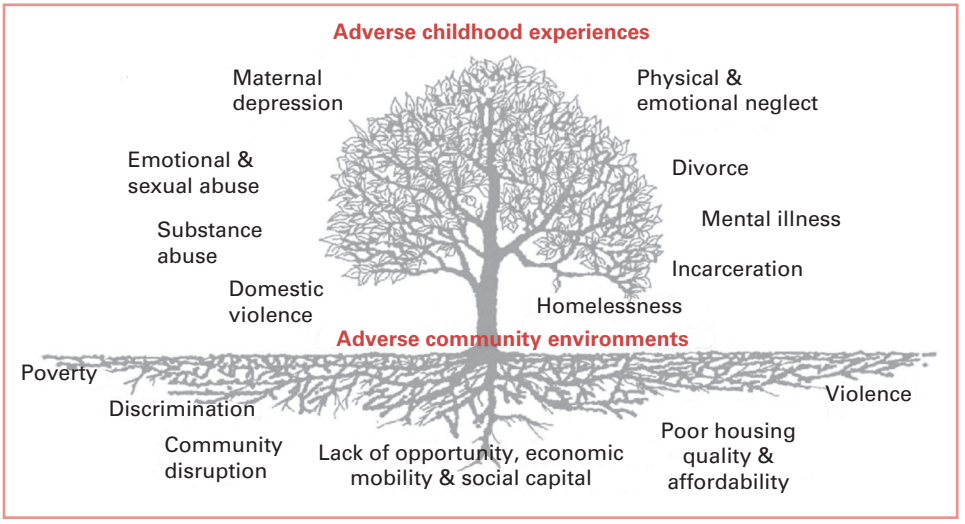

Figure 142.1. Pair of ACEs (adverse childhood experiences) tree.
Reprinted with permission from Ellis WR, Dietz WH. A new framework for addressing adverse childhood and community experiences: the building community resilience model. *Acad Pediatr*. 2017;17(7 suppl):S86–S93.

In the 2012 National Survey of Children's Health, parents in the United States reported that 46% of children had exposure to at least 1 ACE and, depending on the state of residence, 8% to 17% of children had 4 or more ACEs. The most common ACEs parents reported were economic hardship, parental separation or divorce, and parental alcoholism and/or substance abuse. In some states, parental mental illness and community violence were also prevalent. A recent study of more than 700 children, most of whom (67%) had experienced 1 or more ACEs and 12% of whom had experienced 4 or more ACEs, found that increased ACE score correlated with increased risk of learning and behavior problems and obesity. This correlation was especially marked for learning and/or behavior problems. Children with 4 or more ACEs were 32 times more likely to have learning and/or behavior problems in school than children with no ACEs.

Clinical Presentation

In a clinic setting in which a physician might see 20 patients per day, at least 2 patients may have experienced at least 4 ACEs. In the pediatrics clinical setting, a patient may be actively experiencing the pair of ACEs. The presentation is variable and related to the child's developmental stage, temperament, and family protective factors. A high number of ACEs in childhood may present as behavior concerns at any age (eg, aggression in a toddler, attention-deficit/hyperactivity disorder [ADHD] in the school-age child, and promiscuity or drug use in the teenager); developmental delays in the preschool-age child and learning concerns in the school-age student; physical symptoms, including functional symptoms (eg, stomachache, headache, poor sleep); and medical or psychiatric conditions (eg, poorly controlled asthma, encopresis, depression, suicidality). Nonadherence to medical treatment plans and missed appointments may also be signs of family adversity (Box 142.3).

Box 142.3. Presenting Signs of Adverse Childhood Events in Pediatric Practice

Learning/Behavior

- Attention-deficit/hyperactivity disorder
- Aggression
- Classroom disruption
- Speech delay
- Tantrums

Mental Health

- Anxiety
- Depression
- Substance use
- Suicidality

Other Health

- Missed appointments
- Morbid obesity
- Poorly controlled chronic illness
- Treatment nonadherence

Pathophysiology

Early childhood experiences influence the neural wiring for learning, memory, and behavior, and they shape the evolution of the neuroendocrine, autonomic, metabolic, and inflammatory systems. The architecture of the brain is built over time through experiences the child has in the child's family and community environments. In the first few years after birth, new neural connections (ie, synapses) are formed every second, and the brain reaches 80% of its adult size by age 3 years. Responsive interactions between child and caregiver are the building blocks that support healthy brain and body circuitry. Learning occurs when certain neural connections are strengthened resulting from use and others are pruned away because of lack of stimulation.

After the early childhood years, another major critical period of brain development occurs during adolescence, from puberty through the young adult years. Especially important during this time is the development and maturity of the prefrontal cortex of the brain. The prefrontal cortex has been dubbed "the CEO" of the brain, because it is the area responsible for executive function skills, including impulse control, attention, working memory, organization, planning, and mood modulation. Unbuffered stress and insults such as tobacco, alcohol, and other substance use during this second sensitive period of brain development can adversely affect the wiring of the prefrontal cortex.

During childhood and adolescence, the wiring of the brain's stress regulation system is under construction to respond in positive, tolerable, or toxic ways to perceived threats in the environment. When a person perceives a threat to his, her, or their safety, the brain and body adaptively release the hormones cortisol, norepinephrine, and epinephrine in preparation for a "fight, flight, or freeze" response. This evolutionarily conserved hormonal response results in the physiologic changes that allow the person to respond to the stressor. With a *positive stress response*, the elevations in heart rate, blood pressure, and hormone levels are short-lived and return to normal after the threat has passed. With a *tolerable stress response*, stronger threats may produce a more prolonged but not damaging response, because of the presence of buffers, such as the presence of supportive adults in a child's life. With a *toxic stress response*, however, the stress response system remains chronically activated, resulting in changes in brain and body physiology (Figure 142.2). In the absence of buffers assuring the child he or she is safe, exposure to ACEs can trigger the excessive activation of the stress response that is the biologic mechanism by which social and environmental circumstances result in detrimental effects on health (Figure 142.3).

Differential Diagnosis

Recognition that childhood adversity is common and pervasive should lead the health professional to consider ACEs-related trauma and consequences of excessive stress activation in the differential diagnosis of many common childhood reports. The child who presents with learning or behavior concerns (eg, aggression, excessive tantrums, speech delay, classroom disruption, ADHD); mental health problems (eg, depression, suicidality, substance abuse); and other health issues (eg, morbid obesity, poorly controlled chronic

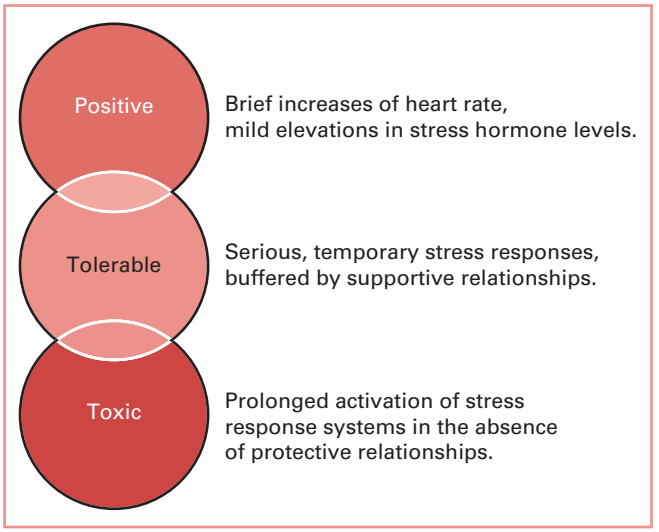

Figure 142.2. Levels of stress response.
Reprinted with permission from Center on the Developing Child at Harvard University. http://developingchild.harvard.edu

illness, treatment nonadherence, missed appointments) should undergo ACEs screening to help inform the child's treatment plan.

Evaluation

Because ACEs occur across all populations, routine screening would be ideal. Addressing exposure to traumatic events in a primary care practice can be considered challenging, however. Barriers to screening may include the health professional's lack of time during the office visit, lack of comfort in addressing sensitive family topics, and lack of training in managing positive screening results, as well as lack of community resources for family linkage. Starting such a screening practice can seem daunting. As a first step, the pediatrician may consider ACEs screening for the child with unexplained somatic symptoms, behavioral concerns, or changes in educational or socioemotional functioning. Sometimes the right question to ask is not, "Why are you behaving this way?" but, "Can you tell me what has happened to you?" For the younger child, the physician may ask the caregiver, "Since the last time I saw your child, has anything really scary or upsetting happened to your child or anyone in your family?" This same question may be addressed directly to the older child. The pediatrician must take the time to understand what has happened to the child before trying to "fix" the problem.

The practice with interest in implementing broader screening can use any of several standardized measures to identify factors that put children at risk for ACEs, including screenings for maternal depression, food insecurity, parental substance abuse, and domestic and/or community violence. Currently, no universally agreed on standard screening instrument exists for ACEs exposure in pediatrics. However, several tools have been developed for a pediatric population that can help the medical home in identifying these children, including Bright Futures Pediatric Intake Form, Center for Youth Wellness ACE-Q materials, Survey of Well-being of Young Children (SWYC), and Safe Environment for Every Kid (SEEK) questionnaire (Table 142.1). These and other clinical assessment

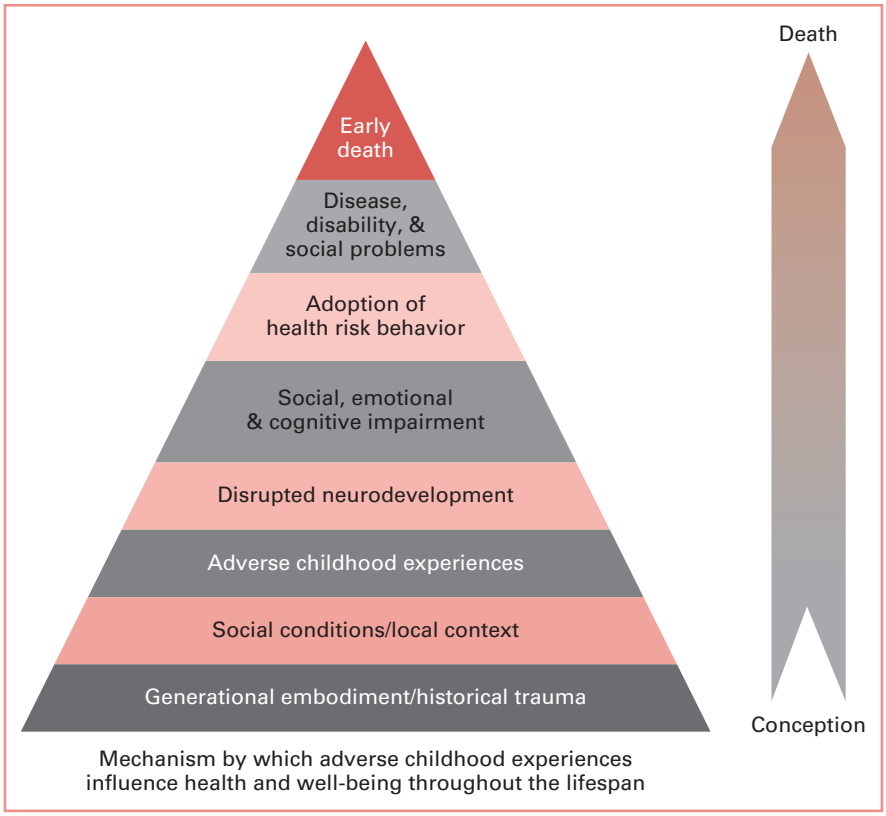

Figure 142.3. Adverse childhood experiences pyramid.
Reprinted from Centers for Disease Control and Prevention. About the CDC–Kaiser ACE Study. The ACE pyramid. CDC.gov website. www.cdc.gov/violenceprevention/acestudy/about.html.

Table 142.1. Adverse Childhood Experiences Screening Tools

Screening Tool	*Pros*	*Cons*
ACE Questionnaire	Brief	Not developed for pediatrics
Bright Futures Pediatric Intake Form	Developed for pediatrics	Not validated for research
Center for Youth Wellness ACE-Q materials	Developed for pediatrics	Not validated for research
Survey of Well-being of Young Children (SWYC)	Developed for pediatrics; validated	Longer
Safe Environment for Every Kid (SEEK)	Developed for pediatrics; validated	Longer; training required to administer

Abbreviation: ACEs, adverse childhood experiences.

tools are available on the American Academy of Pediatrics website, The Resilience Project (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Resilience-Project.aspx). Practices that implement ACEs-related screening should identify supportive resources in the local community with which to link families with at-risk screening results. Additionally, the physician should evaluate the family for protective factors that contribute to resilience in the presence of adversity (Box 142.4).

Management

Recognition of the role of ACEs as contributors to the presenting symptom facilitates the development of a more comprehensive treatment plan. *Trauma-informed care* in the medical setting involves delivering services in an environment of physical and emotional safety for families and health professionals, helping caregivers and children gain a sense of agency and control in their lives by sharing information with them, and involving the caregivers and children as active participants making decisions about the treatment plan. Children need to regain expectations that they are safe and lovable and that life has meaning. Attention to nutrition, exercise, sleep hygiene, and daily routines are important, as is addressing the psychosocial needs of children and their parent(s)/guardian(s).

Educating the family on the role of ACEs in the child's condition and providing referrals to social supports in the community, parenting programs, and psychotherapy can be added to the standard medical treatment of the presenting condition. Examples of evidence-based mental health programs for children who have experienced ACEs include Parent-Child Interaction Therapy and trauma-focused cognitive behavioral therapy. Complementary treatments, such as therapeutic yoga, can be considered if available in the area. An intergenerational approach will benefit parents who themselves have experienced ACEs and who may exhibit reduced parenting capacity or maladaptive responses to their children. Programs that encourage responsive relationships, reduce external stressors, and build executive function skills for adults and children can be transformative. Follow-up in the pediatrician's office is important, because the medical home can be a source of stability and support for families affected by trauma.

Sometimes the stressors that families experience can be overwhelming for the health professional as well. Acknowledging the effect on physicians and staff is part of a trauma-informed approach.

Box 142.4. Family Protective Factors That Contribute to Resilience in the Presence of Adversity

- Close relationships
- Parental resilience (bounce back)
- Awareness and application of positive parenting and child development practices
- Social connections (eg, friends, relatives, community members)
- Concrete support in times of need
- Sense of purpose (eg, faith, culture, identity)
- Individual competencies (eg, problem-solving skills, self-regulation, sense of agency)

Prevention

Primary prevention efforts to reduce the effect of ACEs on health involve reducing exposures to stressors and building buffers at multiple levels: society, neighborhood, school, family, caregiver, and child. Laws protecting civil rights, family leave policies, earned-income tax credits for working parents, home visiting programs, early childhood education, neighborhood safety, trauma-informed schools, afterschool programming, and positive parenting programs are examples of multilayer efforts to increase buffers in the community. Examples of evidence-based parenting programs include The Incredible Years, Circle of Security, and Guiding Good Choices. In the pediatric office, care for the parent or guardian during the well-child visit can include promoting bonding and secure attachment, providing guidance on normal child development and challenges, sharing coaching strategies on managing crying and misbehavior, and promoting literacy. The pediatrician can participate in the Reach Out and Read literacy initiative (see Chapter 34) and may wish to encourage the parent or guardian to use the Vroom child development mobile application, if possible. For the child, building resilience requires opportunities to build a sense of self-efficacy and self-regulatory capacities. For the family, faith, hope, and cultural traditions can be sources of strength (Box 142.5).

Secondary prevention efforts, such as screening for maternal depression, hostile parenting, food or housing insecurity, and developmental delays, and providing linkages to community resources are within the pediatrician's scope of practice in supporting a child's optimal development.

Prognosis

Adverse childhood experiences do not dictate the future of the child. Although it is easier to build neural connections right the first time rather than trying to fix them later, the potential for neuroplasticity

Box 142.5. Opportunities for Primary Prevention of Adverse Childhood Experiences

Society
- Civil rights laws
- Family leave policies
- Earned-income tax credits

Neighborhood
- Safety
- Early childhood education
- After-school programs

Pediatrician
- Promotion of bonding/secure attachment
- Guidance on normal child development (eg, Vroom app)
- Strategies for managing crying and misbehavior (eg, Zero to Three videos)
- Promotion of Literacy (eg, Reach Out and Read)

Family
- Home visiting programs
- Parenting programs
- Cultural or faith traditions

Child
- Developing self-regulation (eg, making choices; play games such as Simon Says, Red Light Green Light)
- Promoting self-efficacy (eg, goal setting, ability to learn from mistakes, praise effort, build on strengths)

exists throughout the life span. Children survive and even thrive despite the trauma in their lives. For these children, ACEs are counterbalanced by protective factors. Adverse events and protective factors experienced together have the potential to foster resilience. Knowledge of what constitutes resilience in children is evolving, but it is known that several factors are related to such protection, including cognitive capacity, healthy attachment relationships, motivation to learn, self-regulation skills, and supportive environments. The 7 Cs of resilience coined by Kenneth Ginsburg, MD, are competence, confidence, connection, character, contribution, coping, and control. Resilience is built over time, and the presence of a stable, caring adult in a child's life is critical in this process. These relationships provide the buffer and give children a sense of value: "I matter."

Additionally, differential individual susceptibility plays a role, with some children more affected than others by their environmental circumstances. It is important to help parents and guardians recognize that children in the same household can respond differently to the same event. Future directions for research include identifying children who would benefit most from tailored interventions. Studies of individuals living in the world's "Blue Zones" of longevity have found that lifestyle factors can also help mitigate effects of childhood adversity, including being physically active; having healthy eating habits, social ties, and family support; and faith.

CASE RESOLUTION

A thorough family and social history reveals that Chris currently lives with his mother, stepfather, and 2 younger sisters in supportive housing. The stepfather has known Chris since he was an infant and has been married to his mother for the past 8 years. The family became homeless 4 years previously when the stepfather lost his job. Since that time, they have lived in various shelters, in their car, and with relatives until being placed in housing 6 months previously. The family continues to struggle with financial hardships and food insecurity. Chris's biologic father has been incarcerated since Chris was 2 years old; his father has a history of domestic violence, substance abuse, and ADHD. Chris's mother has a history of learning issues and depression. Chris has attended at least 6 different schools in the past 4 years and has been at his current school for 4 months. His stepfather recalls that Chris had an Individualized Education Program (IEP) a few years previously, but because of the family's frequent moves, his IEP records have been lost and the school been unable to locate them either. Chris had been having behavioral outbursts for approximately 2 years but had been doing relatively well this year, until the recent hitting incident. He looks forward to going to school. His teacher likes him and has been working with him outside of class to help remediate his reading skills.

You review the history and conclude that Chris has an ACE score of 5; he has experienced all 5 household dysfunction criteria. Additionally, he has a history of homelessness, a factor that is not included in the original ACEs profile. Further exploration of protective factors is warranted, but based on initial intake such factors include Chris's positive relationships with his stepfather and his teacher as well as the family's access to supportive housing. The physical examination is normal, as is the urinalysis. You discuss behavioral management strategies for the nocturnal enuresis. To further understand Chris's attention and behavior concerns, you provide the family with the National Initiative for Children's Healthcare Quality Vanderbilt Assessment Scale to be completed by his teacher and parents. To address his learning concerns, you write a letter to request an evaluation for an IEP. You provide a book to Chris and remind him to read 20 minutes every night. The family is already connected to a local community housing support agency, and through this agency, Chris is receiving in-home therapy and his parents are receiving parenting support services. You schedule a follow-up visit to further assess and treat his bedwetting, attention, behavior, and learning concerns.

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CHAPTER 143

Commercially Exploited Children and Human Trafficking

Jordan Greenbaum, MD

CASE STUDY

At age 17 years, Joe ran away from home to escape family violence and maternal substance use. He had no money or resources while living on the street, so he exchanged sex acts for money, food, shelter, clothes, and drugs. Many of the other homeless youth were doing the same, and they provided support to each other. None of the youth was operating under the control of a "pimp." Joe continued to engage in "survival sex" until age 19 years, at which time he met a man who promised to get him more clients and money. Joe agreed to the arrangement and stayed with this man for 1 year, giving him 30% of what he earned. Eventually Joe made the decision to stop this work, but when he announced this to his "friend," the man beat him and told Joe he could not quit and must continue selling sex to "earn his keep." Further, the man threatened to tell Joe's family that he was selling sex unless Joe agreed to deliver drugs to a dealer in another city. Joe's involvement in commercial sex and the drug trade continued for 6 months. Today, Joe arrives at your clinic and requests testing for HIV and sexually transmitted infections.

Questions

1. What are some of the risk factors associated with a trafficked individual?
2. What is the typical sequence of events that precede becoming trafficked?
3. In a patient, what are possible indicators of human trafficking?
4. What is the best means of approaching a patient who may be experiencing sex or labor trafficking?
5. Is Joe, the patient in the scenario, being trafficked? Why or why not?

Epidemiology of Child Trafficking

According to United States federal law, *child sex trafficking* occurs when an individual engages a minor (younger than 18 years of age) in a commercial sex act (ie, any sexual act that involves an exchange of something of value); no force, fraud, or coercion is necessary. Thus, children or adolescents exchanging sex for food or money to purchase luxury items are trafficked persons, as are those who are engaged in the production of child sexual exploitation images (formerly referred to as "child pornography") and those working in strip clubs. Neither involvement of a third party in the sexual transaction nor transportation of the individual from 1 place to another is necessary to constitute child sex trafficking. However, once the youth turns 18 years of age, the adult definition of sex trafficking applies, which requires the demonstration of force, fraud, or coercion as a means of exploitation. Thus, Joe, the patient presented in the case study, was being sex trafficked while he was a minor (ie, exchanging sex to fill critical survival needs), but once he turned 18, the survival sex was no longer considered "trafficking" because no obvious force, fraud, or coercion was involved. When Joe is working for the "friend" and that person assaults him when Joe wants to leave commercial sex work, Joe becomes a victim of adult sex trafficking because force has been used; Joe's previous "consent" in the commercial sexual activity becomes irrelevant.

Throughout this chapter, the term "victim" is used in its objective, legal sense as indicating a person who has been harmed as a result of some event or action or who has suffered as the result of someone else's actions. The term does not refer to how the individual may feel or perceive himself or herself as a result of the event or events and is not intended to be used to label that individual.

Both *child labor trafficking* and *adult labor trafficking* involve recruiting, harboring, transporting, providing, or obtaining an individual for labor using force, fraud, or coercion. This may involve either use of physical or psychologic tactics or abuse of the legal system in an effort to force an individual to work (ie, involuntary

servitude). It may also involve charging an individual an exorbitant amount and forcing the individual to work off the debt (ie, debt bondage). Children and adults may be trafficked in a wide variety of industries, both legal and illegal. Some of the more common industries include domestic servitude (eg, nanny, live-in maid), construction, agriculture, nail salons, sales crews, the hospitality industry, restaurants, and peddling or begging. Individuals may be trafficked in criminal activities, such as drug dealing or theft. In some cases, especially among females, both labor and sex trafficking occur. Joe is experiencing both labor and sex trafficking: he is coerced (via threats) to engage in illegal drug activity and is being forced to engage in commercial sex work.

Reliable prevalence rates for labor and sex trafficking are elusive, given the criminal nature of the activity, the reluctance of trafficked persons to report the crime, the lack of a centralized database and consistently used definitions, and the fact that many individuals do not realize they are being exploited. Statistics of identified trafficked persons suggest that girls are more vulnerable to sex trafficking than boys, although reporting bias, underrecognition, and reluctance to report likely contribute to the lack of identified males. Both males and females are vulnerable to labor trafficking, especially in the adolescent age group. Risk factors for child trafficking are described in Table 143.1. Research consistently demonstrates very high rates of prior abuse and neglect, as well as runaway/homeless status and involvement with child protective services and/or juvenile justice systems among sex-trafficked youth; these factors are very likely relevant to labor trafficking as well, although less research is available on this type of exploitation. Poverty, natural disasters, forced migration, and dysfunctional family situations may drive a child into a labor or sex trafficking situation. Exploitation may occur at any age, although adolescents age 13 to 17 years tend to be overrepresented. Limited research suggests that intrafamilial trafficking may involve younger children, on average, than trafficking involving non-family members, and may involve children in a wider age range. Trafficking occurs among children of all races, ethnicities, religions, cultures, and socioeconomic statuses.

Table 143.1. Risk/Vulnerability Factors for Child Trafficking: Socioecological Model

Level	*Description*
Individual	History of sexual violence; physical abuse and/or neglect Homeless, runaway, or throwaway status[a] Involvement with juvenile justice system and/or child protection services Substance misuse Untreated mental health and/or behavioral problems LGBTQ+[b] status Migration (especially unaccompanied minors) Lack of official documents (eg, immigration document, card, or visa, birth certificate)
Relationship	Intimate partner violence Family poverty and/or unemployment Family dysfunction Limited education Parent/guardian and/or peers involved in commercial sex work or purchasing sex Intolerance of LGBTQ+ status Forced migration
Community	Tolerance of sexual exploitation Lack of community resources High crime rate (especially organized crime) Tourism and/or transient populations in area Lack of awareness about child trafficking Adult sex work in area Gang activity
Societal	Gender-based violence and discrimination Cultural attitudes and/or beliefs Natural disasters Political and/or social upheaval, military conflict Law enforcement and/or political corruption Lack of acknowledgment of child rights

[a] Throwaway status: child told to leave home or told not to return home.

[b] Lesbian, gay, bisexual, transgender, queer/questioning, or other sexual minority (see Chapter 57).

Clinical Presentation

Research suggests that a large proportion of identified trafficked persons, especially those who are involved in sex trafficking, seek health care during or shortly before their period of exploitation. In 1 study of adolescent/young adult trafficked persons, 82.5% were seen at the local children's hospital within the year prior to identification. In another study of sex-trafficked adolescent females, 42.9% had received health care within the 2 months prior to identification. Numerous studies from around the globe have documented a wide array of adverse physical and mental health effects associated with trafficking, including physical injury (from work-related accidents, to physical or sexual assault); HIV and other sexually transmitted infections (STIs); nonsexually transmitted infections, such as tuberculosis; malnutrition and dehydration; unplanned pregnancy and complications thereof; substance misuse; chronic pain; posttraumatic stress disorder; depression and suicidality; somatic symptoms; and behavioral problems.

Given the plethora of adverse health consequences, trafficked children and youth may present with any of a wide variety of chief concerns. Such individuals may present for evaluation of sexual or physical assault (often with a false history provided), requests for STI or pregnancy testing, other genitourinary symptoms, behavioral issues, attempted suicide, drug intoxication, or sexual abuse. They may present with chronic medical conditions that are unrelated or only indirectly related to their exploitation (eg, asthma exacerbation from lack of access to the patient's medications). Evidence of adverse health effects may be noted incidentally, such as a finding of scarring from cigarette burns on physical examination.

Care may be sought in a variety of health care settings. Although studies show a large proportion of trafficked persons seeking care

in emergency departments and reproductive care clinics (especially Planned Parenthood), trafficked persons may also attend clinics for teenagers, community health centers, school clinics, private pediatrician practices, specialty clinics, mental health clinics, psychiatric hospitals, dental practices, or surgical practices. Trafficked children and adolescents may present to a health care facility alone or with peers (who may be traffickers, other survivors, or friends unaware of the exploitation). They may be accompanied by a parent or other relative (who may or may not be a true relative and who may or may not be involved with the trafficking), an employer, or some other adult.

Trafficked persons may be very reluctant to disclose their exploitative situation to health professionals. This may be secondary to distrust of authority, language barriers, shame, guilt, fear of retaliation by a trafficker, fear of arrest or deportation, fear of being sent back to foster care, or a desire to protect the trafficker, whom the trafficked person feels is looking out for his, her, or their best interest. In the latter case, a patient may have developed strong "trauma bonds" with the trafficker related to the highly stressful, manipulative character of the relationship. These bonds may prevent the trafficked person from realizing the exploited status and result in the trafficked person actively defending the trafficker. In other cases, a patient may not perceive the situation to be exploitative because it has been normalized or because the individual is unaware of his or her human and legal rights.

If spontaneous disclosure by a patient is unlikely, presenting symptoms may be varied, and a patient may or may not be accompanied by a trafficker, how does a health professional recognize a trafficked child or youth, or one who is at high risk for exploitation? The health professional should be aware of risk factors for trafficking and some of the potential indicators that may be present at the time of the health visit (Table 143.2). It is important to note that the indicators are nonspecific and may be absent in a given case.

Evaluation

A traumatized patient, such as a patient who has experienced sex or labor trafficking, needs a trauma-informed approach to health care. According to the Substance Abuse and Mental Health Services Administration, the trauma-informed approach incorporates a realization that traumatic experiences may profoundly affect the individual, family, group, organization, and community. Trafficked children and youth often have experienced repeated severe trauma, both before and during their period of exploitation. Their feelings, attitudes, and behaviors are shaped by these experiences; they interpret the world around them, including the words and behaviors of others, through a trauma lens. Stress reactions and behaviors developed to survive in a dangerous situation may lead traumatized patients to behave in ways that, to a health professional, appear maladaptive. A trauma-informed physician can recognize signs of trauma and trauma-related stress and respond in a supportive, nonjudgmental, and empathic manner. Such physicians demonstrate openness, respect, and cultural sensitivity. They take steps to increase the patient's sense of safety (physical and psychological), trust, and resilience. Additionally, these health professionals

Table 143.2. Potential Indicators of Child Trafficking

Evaluation	*Indicator*
Initial presentation	Patient presents either alone or with multiple peers requesting treatment Patient or companion gives inconsistent or implausible history Patient appears depressed, fearful, or quite anxious Patient is unfamiliar with the city or town, cannot give address where staying Patient's companion is: Domineering and apparently intimidating to the patient Speaking for the patient or trying to insist on translating for the patient Reluctant to answer health professional's questions, impatient for discharge Reluctant to leave patient alone with the health professional Is not the patient's guardian
History	Sexual, emotional, or physical abuse or neglect Runaway, homeless, or throwaway status[a] Involvement with child protective services or juvenile justice system LGBTQ+ Behavior problems and/or mental health history >5 sex partners Multiple prior sexually transmitted infections Pregnancy (or fathering a child) Forced migration Patient is an immigrant and not in control of official documents Relatives and/or peers participate in commercial sex work, whether selling or buying
Physical examination	Flat affect; withdrawn or hostile/aggressive Signs of posttraumatic stress disorder (eg, dissociation, hypervigilance, triggered anxiety responses) Patterned injuries or injuries in protected areas (neck, ears, torso, upper arms, thighs) Evidence of anogenital trauma or infection Signs of substance use/misuse Signs of malnutrition, dehydration Certain types of tattoo (eg, sexual inuendo, street name, gang insignia) Patient inappropriately dressed for weather Patient with large amount of cash, a few expensive items, multiple cell phones

[a] Throwaway status: Child or youth is told to leave home or told not to return home.

Abbreviation: LGBTQ+, lesbian, gay, bisexual, transgender, queer/questioning, or other sexual minority.

make every effort to minimize re-traumatization associated with the health visit. They use a *victim-centered approach*, in which the best interest of the patient drives all questions, discussions, plans, and activities. Key concepts of a trauma-informed approach to care are presented in Table 143.3.

Effectively working with trafficked individuals involves respect for fundamental human rights, including respect for the patient's race/ethnicity, sex, gender, sexuality, religion, social status, and cultural beliefs, without demonstrating bias or discrimination. It involves respecting a patient's right to information that is provided in an understandable manner and the patient's right, as developmentally appropriate, to actively participate in the patient's own care. Additionally, it involves respecting the patient's rights to privacy and confidentiality.

Table 143.3. Concepts of a Trauma-Informed Approach to Care

Concept	*Attitudes and Behaviors*
Screen for trauma (ie, human trafficking)	The physician is aware of risk factors and potential indicators of human trafficking and asks questions to assess the level of risk for exploitation. *The goal is not necessarily to obtain a disclosure but to assess risk so as to be able to respond appropriately and offer resources.* If the health professional is a mandated reporter, the professional's response to a patient deemed to be at high risk for exploitation is the same as for a patient who is known to be trafficked; that is, report to authorities and offer resources/referrals and anticipatory guidance. Having certainty about exploitation is not required, and pushing a patient to disclose is not appropriate.
Safety	The health professional takes steps to increase the patient's physical comfort (eg, uses private, youth-friendly room; inquires about the patient's basic physical needs) and decrease stress and anxiety. The health professional ensures the physical safety of the patient and staff and interviews the patient with the companion(s) out of the room.
Trust	The health professional takes time to build rapport; maintains nonjudgmental, empathic attitude; actively listens to the patient; demonstrates interest in learning about the patient's situation; and avoids making assumptions.
Respect	The health professional demonstrates respect by explaining what the professional wants to do and why (eg, reasons for asking questions, conducting examination, ordering tests), seeks permission (truly informed consent) for every step of the health visit, and accepts the patient's perspective and decisions without argument or applying pressure to change the patient's mind.[a] The health professional listens more than talks.
Transparency	The health professional explains limits of confidentiality early in the medical interview, uses simple language when explaining the process of the visit and suggestions for treatment, and thoroughly explains the process of reporting to authorities (as applicable).
Strengths-based approach	The health professional seeks to identify patient strengths (ie, resilience), facilitates patient awareness and appreciation of the patient's own strengths, and acknowledges that the patient is the expert on himself or herself.
Patient engagement and empowerment	The health professional actively encourages patient questions, discussion and suggestions for care; asks the patient questions about the patient's own view of the situation and what might help improve it; solicits feedback on the health professional's ideas for treatment and referral; and offers the patient choices and control whenever possible throughout the health care visit.
Cultural sensitivity	To the extent possible, the health professional is aware of and sensitive to cultural differences between the professional and the patient; and the health professional takes steps to understand the patient's cultural perspective and to respect cultural preferences when possible. The health professional asks questions about how the patient perceives relevant problems and solutions as well as the patient's views on health care and on the patient's current life situation.
Emphasis on minimizing re-traumatization	The health professional asks only the questions necessary to guide the examination, evaluation, anticipatory guidance, treatment, and referrals and to assess safety; monitors the patient for verbal and nonverbal signs of distress during the medical interview and examination; takes steps to reassure and support the patient; and has a plan in place to manage major psychological distress.
Available resources/referrals	The health professional or a designee creates a list of community, regional, and national resources to provide to the patient; establishes relationships with community victim service agencies and knows their services and eligibility requirements; and arranges a "warm hand-off"[b] to the referral agency when possible.

[a] Respecting a patient's decision about evaluation and treatment assumes the absence of life-threatening health issues that require emergent care, such as uncontrolled bleeding.

[b] In the "warm hand-off," the health professional directly contacts the victim service agency to discuss and arrange the referral or assists the patient with making contact while in the health facility (eg, allowing patient to use the telephone in a private room, providing the agency number, offering assistance as needed).

If a patient presents with risk factors for, potential indicators of, or other concerns for possible trafficking, the health professional will need to ask additional questions to assess risk (with the patient's assent). Questions to consider are shown in Box 143.1.

If the patient is willing, it is helpful to include in the medical history a detailed reproductive history, including information such as gender identity and sexual orientation, number of sexual partners, age at first sexual intercourse, and use of condoms. Addressing these issues opens the door for anticipatory guidance, helps indicate what resources or referrals may be necessary, and assists the health professional in gauging risk for sexual exploitation. Because of the very high rates of posttraumatic stress disorder and depression among victims of sex and labor trafficking, a brief mental health screening is appropriate to determine whether emergency psychiatric intervention is necessary. Screening for substance misuse is also indicated.

With patient consent, a thorough head-to-toe physical examination will allow assessment of nutrition, hydration, and any evidence of chronic disease. The trauma-informed approach extends to the physical examination, and it is important that the health professional explain each aspect of the examination and proceed slowly, being mindful of any sign of distress from the patient. Thorough documentation of extragenital and genital injury is important; this is best done with photographic documentation and a thorough written description of injuries. A chaperone (not the individual[s] accompanying the patient) must be present for the examination to monitor the patient for signs of distress. It is common for sex-trafficked youth to experience anxiety and distress with the anogenital examination, and if episodes of the patient's victimization have been recorded in the past, the use of cameras or videorecorders during the examination may trigger additional stress. For suspected sex trafficking and cases of labor trafficking that might also involve sexual exploitation and/or assault, an anogenital examination should be offered to the patient. If the health professional is not confident in conducting a detailed anogenital examination, it is appropriate to contact a specialist, such as a sexual assault nurse examiner or a child abuse pediatrician.

Box 143.1. Sample Questions for Assessing Risk for Trafficking

- I see many kids who live on the streets or run away from home, and most of them have a very hard time obtaining the money they need to survive. Many have to resort to exchanging sex to get food, shelter, money, drugs, or other things. Do you know anyone who has had to do that? Have you ever felt like you were in that position? Can you tell me about that?
- Has anyone ever offered to pay you to have sex? If so, do you feel comfortable telling me about that?
- Can you tell me a bit about your job? Maybe take me through a typical day for you?
- Are the working arrangements you have now at your job what you expected they would be? If not, can you tell me a bit about that? How are they different from what you expected?
- Has there ever been a time when someone asked you to do or forced you to do something that made you feel uncomfortable? Do you feel comfortable telling me about it?

Thorough documentation of anogenital findings is necessary, with special attention to the hymen and perihymenal structures in females, because this is a common area of injury in sexual assault. In many cases, however, the anogenital examination is completely unremarkable, with no evidence of injury, even if the patient reports genital trauma and bleeding in the past. The adolescent hymen and the anus are capable of considerable distention to accommodate objects larger than their resting diameter without sustaining injury. When injury does occur, it typically heals rapidly (within days to a few weeks) and completely, without scarring. Thus, a negative anogenital examination neither supports nor refutes the possibility of sexual exploitation.

A sexual assault evidence kit may be indicated, depending on the time of the last sexual encounter and the time frame used by the local police jurisdiction for obtaining trace evidence. As with all other aspects of the evaluation, the kit should not be obtained without the patient's assent. Sexual assault evidence kits typically contain detailed instructions. Swabs should only be collected from areas involved in sexual contact. A strict chain of evidence should be maintained when collecting, storing, and submitting the kit to law enforcement.

Once the examination is complete, it is important to discuss the results with the patient and ask if the child or youth has any questions or concerns about his or her body. Trafficked individuals may harbor anxiety about a variety of issues, including possible infertility, future health, or possible permanent damage from work-related injuries and toxic conditions.

Testing for pregnancy and STIs should be offered, following Centers for Disease Control and Prevention guidelines for STIs. This includes testing for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, syphilis, HIV, and hepatitis B virus. Consideration should also be given to testing for other infections as appropriate, such as herpes simplex virus, hepatitis C virus, tuberculosis, and infections endemic to the patient's home country. Laboratory tests for malnutrition or vitamin and mineral deficiency may be indicated. Depending on the medical setting, vision and hearing tests should be considered, as well as administration of vaccines and discussion of contraception (especially long-acting, reversible contraception). The health professional providing care for a foreign national trafficked individual may obtain guidance on medical screening and care for immigrant children from the Centers for Disease Control and Prevention as well as the American Academy of Pediatrics resources *Red Book* and Immigrant Child Health Toolkit.

Because of the high risk of ascending infection and the likelihood that the patient will not be able to attend a follow-up appointment, it is advisable to offer prophylaxis for *N gonorrhoeae*, *C trachomatis*, and *T vaginalis*. Emergency contraception should be offered to females. HIV post-exposure prophylaxis should be considered in this very high-risk population; however, it is not suitable for all patients, especially those who are unable to comply with a rigorous regimen of daily medications. The risks and benefits should be discussed with the patient, and the health professional may seek advice from infectious disease specialists.

Documentation is an important aspect of the patient visit, and all efforts should be made to adopt strategies to protect privacy and confidentiality to the fullest extent. These strategies may differ according to facility resources and protocol. The need to document patient history, including risk factors and high-risk behaviors, physical findings, test results, and diagnoses as accurately and thoroughly as possible to ensure optimal continuity of care must be weighed against the possibility of a trafficker gaining access to the patient's records (eg, forcing the patient to access the electronic medical record, reading discharge summaries) and possible stigmatization associated with exploitation, especially sexual exploitation.

Management

All reports and referrals should be made with the patient's best interest in mind. Engaging the patient in care planning is critical, because the patient is the expert on the patient's own living situation. Although the health professional must abide by mandatory reporting laws, that individual must also make every effort to advocate for the patient to be treated as a person in need of services, not a criminal in need of incarceration. Not all law enforcement and child service workers have received training on labor and sex trafficking, so some may mistakenly assume the patient is a "child prostitute" who should be punished for engaging in a crime or that the immigrant patient who is in the country illegally should be deported. The health professional may need to explain to these other professionals the victimization and manipulation involved in child trafficking and explain that sex trafficking force, fraud, or coercion are not required for a situation to be labeled sex trafficking.

Most trafficked individuals have a great many needs, ranging from medical and behavioral health (Box 143.2), to housing, food, crisis intervention, immigration assistance, legal assistance, translation assistance, and education and job skills training, as well as family support and services. Multidisciplinary collaboration is necessary to meet these needs, and the health professional plays a critical role in this as well. The health professional may provide direct services and offer referrals to the patient, always seeking consent before taking action. As indicated in Table 143.3, all efforts should be made to make referrals using a warm hand-off. That is, the health professional or other designated staff should directly contact the referral agency or organization to discuss and arrange the referral, or facilitate the patient making contact during the health visit. Possessing a current list of community, regional, and national resources is critical to linking trafficked patients with services. A valuable national resource in the United States is the National Human Trafficking Hotline (1-888-373-7888; https://humantraffickinghotline.org/). The National Hotline has trained staff to assist trafficked individuals and professionals alike, including interpreters for more than 100 languages. Additional assistance may be obtained by contacting state or local law enforcement and anti-trafficking task forces or local child advocacy centers.

A patient may not be ready to accept offers of assistance or may feel it is not safe to do so. Creative means of providing hotline numbers have been proposed, including inserting a small sheet of paper in a tampon container or lipstick holder or entering the National Hotline number into the patient's mobile phone under a fake friend's name. Regardless, it is critical to respect the patient's decision about accepting or rejecting services, making it clear that the child or adolescent is welcome to come to your facility in the future if he, she, or they needs help. If feasible, scheduling follow-up appointments in the medical setting to monitor the patient and continue to build trust and rapport is recommended. Acceptance, support, and an open-door policy increase the likelihood that a trafficked individual will return and accept help if and when the individual feels it is appropriate.

Box 143.2. Common Health and Behavioral Health Needs of Trafficked Persons

Health

- Medical home (accessible, affordable, acceptable) that provides services, such as primary care, immunizations, anticipatory guidance, testing for sexually transmitted infections and HIV, and family planning services
- Obstetrics/gynecologic referral when appropriate
- Examination at a child advocacy center or by a sexual assault nurse examiner
- Care by a health professional specializing in issues related to being lesbian, gay, bisexual, transgender, queer, questioning, or other sexual minority
- Specialist care when appropriate

Behavioral Health

- Assessment for trauma-related symptoms, with trauma-focused therapy as appropriate administered by a trauma-trained provider
- Substance abuse assessment and possibly rehabilitation
- Management of chronic mental health disorders

Prognosis

Re-trafficking of children and youth is common, and it is especially likely in situations in which patients do not view their situation as exploitative. Such individuals may honestly believe their trafficker is their romantic partner and loves them, that their employer is looking out for their best interests, or that "everyone gets treated this way" and their exploitative working conditions are "normal." Alternatively, they may realize they are being exploited but see no way out of the situation and feel they must continue to work until they have paid off their debt. They may be coerced or forced to return to the trafficking situation by those controlling them. It may take several cycles of seeking health care, refusing services, and returning to the exploitative situation before the individual is able to extricate himself, herself, or theirself. When such individuals make the decision to exit their situation, it is critical that they know where they can receive help and support, and the health professional must be ready to provide that help and support.

Prevention

The health professional has a role to play in the prevention of child trafficking. Educating and counseling parents/guardians and patients about risk factors, common recruitment strategies (eg, false

romance, offers of jobs that are "too good to be true"), and possible indicators of child trafficking may help vulnerable youth avoid victimization and enable parents and guardians to recognize early signs of exploitation. Screening patients for risk factors and offering resources to address those factors may prevent victimization (eg, homeless shelters; resources for individuals who identify as lesbian, gay, bisexual, transgender, queer, questioning, or other sexual minority; crisis hotline numbers for teenagers; food pantries; community mental health services; immigrant/refugee organizations; legal aid). At the organizational level, the health professional can advocate for the development of facility protocols to address suspected human trafficking and educate other health professionals about the issues. In the community, the health professional can join multidisciplinary task forces on human trafficking, work with the media to increase public awareness of the issue, and support community organizations that serve trafficked individuals. Finally, the health professional can advocate for policies and laws that increase services for trafficked individuals and improve access to resources that address the social determinants of health, which so often render youth vulnerable to trafficking.

CASE RESOLUTION

You build rapport with Joe by asking him what he likes about himself, what he likes to do, and what famous people he likes. You explain the limits of confidentiality and the voluntary nature of all aspects of the visit. Additionally, you explain that you ask all of your patients questions about their health and background, including some questions that are sensitive, to determine if there is some way you can help them feel better and stay safe. He agrees to answer questions. When you inquire about past medical history, he reports prior gonorrhea and chlamydia infections; he has had "lots" of sexual partners. He has a history of "bipolar" disorder. Joe indicates that he is living with an older man and has a history of running away from home multiple times because of maternal drug use. He appears reluctant to provide details of his living situation or other social history. He does not disclose his sex and labor exploitation to you. You are concerned that he has multiple risk factors for exploitation and inquire more about his time when he was living on the street as a teenager. You ask if he was ever in a position in which he had to consider trading sex for something he needed, such as food or shelter. He hesitates, looks away, and then says, "Yes, but I never did it." He changes the subject and starts talking about his recent genitourinary symptoms. On physical examination you note linear scars on his back, which he vaguely acknowledges as, "from being hit a long time ago." He provides no details. He has a purulent penile discharge that tests positive for gonorrhea.

You talk to Joe about STIs and condom use. You counsel him about the concept of exploitation by those who seek to take advantage of people, either by forcing or coercing them into having sex for money or exploiting them in other types of work. You ask if he would be interested in any information about this and offer to give him the number of the National Human Trafficking Hotline to call if he or a friend ever feels he, she, or they is being exploited. You offer resources for homeless shelters in case he wants to leave his present living situation and ask if there are other community resources he thinks he might need. You arrange for a follow-up appointment in 2 weeks.

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CHAPTER 144

Physical Abuse

Melissa K. Egge, MD, FAAP, and Melissa D. Siccama, MD

CASE STUDY

A 6-month-old boy arrives at the emergency department after becoming limp and nonresponsive at home. The mother states that her son was fine when she left him in the care of her boyfriend before going to the store for cigarettes. When she returned 1 hour later her son was asleep, but then he seized and stopped breathing. The infant is being ventilated by bag-valve-mask ventilation. On examination, the infant is pale and limp. His heart rate is 50 beats per minute, and his blood pressure is 130/80 mm Hg. He has no external signs of injury.

Questions

1. What are the types of injury that may be seen in physically abused children?
2. What are the major lethal injuries associated with physical abuse of children?
3. What are the presenting signs in the child with head injury?
4. What diagnostic studies are indicated in the child with suspected physical abuse?
5. What are the legal obligations of the physician in the area of child abuse?

Physical child abuse was first described in the pediatric literature in 1962 in a classic paper on the battered child syndrome. Child abuse or maltreatment takes many forms, including physical abuse, failure to thrive (Chapter 146), sexual abuse (Chapter 145), emotional abuse, prenatal exposure to substances (eg, drugs, alcohol) (Chapter 148), and *medical child abuse*, the latter of which is a complex disorder previously known as "Munchausen syndrome by proxy" in which parents confabulate or create a medical condition in their child.

The nature and extent of inflicted injuries are variable and may include bruises, burns, fractures, lacerations, internal hemorrhage, and ruptures. The physician must be aware of the legal obligations related to the suspicion of child abuse. It is the responsibility of the physician to assess the nature of the injuries, initiate appropriate medical therapy, and determine if the history offered is consistent with the medical findings.

Epidemiology

It is estimated that the rate of childhood victimization in the United States is 1 in 7 and that approximately 15% to 20% of these children suffer some form of physical abuse. Certain factors are associated with physical abuse. Most victims are young children; two-thirds are younger than 3 years and one-third are younger than 6 months. Caring for young children is frequently demanding, so crying infants and toddlers undergoing toilet training are particularly at risk for abuse. Factors such as lower socioeconomic status, substance abuse, poor parenting skills, and domestic violence place children at increased risk for abuse.

Clinical Presentation

Children who have been physically abused present with injuries that range from nonsevere to lethal (Box 144.1). Visible bruises, bites, and burns may be noted. An infant may initially present with a sentinel injury, a minor injury that is initially underappreciated by the nonoffending caretaker and often the physician. Examples of sentinel injuries include a bruise in a pre-mobile infant, subconjunctival hemorrhage, and frenulum injury. Sentinel injuries should be considered warning signs of future, more severe abusive injury. A child may also have symptoms related to fracture, such as crying or refusal to walk or move an extremity. The more severely injured child may present with seizure, apnea, shock, or cardiopulmonary arrest.

Box 144.1. Diagnosis of Physical Abuse

- Bruises
- Bites
- Burns
- Fractures
- Intracranial hemorrhage
- Intra-abdominal hemorrhage
- Brief resolved unexplained event
- Retinal hemorrhage
- History that changes
- Injuries not explained by history

Pathophysiology

Injuries in children who experience physical abuse are the result of direct trauma inflicted on the children. Abusive parents often have unrealistic expectations of their children, resulting in frustration and abuse when the child does not meet the expectations. Parents who have often been victims of abuse themselves know only corporal punishment as a disciplinary modality. These parents often exhibit poor impulse control; they do not intend to harm their children but rather desire to alter their child's behavior. As a result, sometimes the outcome is unexpected.

Head injuries, the most deadly form of abuse, may result from a direct blow to the head or from rotational head movement (eg, shaking). Classically, a crying infant is vigorously shaken and experiences diffuse axonal injury or intracranial hemorrhage. In particular, subdural hemorrhage may occur from shearing of the bridging veins. The infant may also become apneic during or after the trauma. Seizures, cerebral edema, hypoxic brain injury, and retinal hemorrhages may also occur. Such injuries are frequently associated with a fatal outcome or long-term damage to the central nervous system.

Abdominal trauma is the second most common cause of fatal child abuse and typically is caused by a direct blow to the abdomen. Skeletal fractures result from multiple different types of traumatic forces to the bones. Rib fractures are most classically associated with the head trauma of shaking and are caused by compression of the ribs by the hands holding the infant or child.

Differential Diagnosis

When evaluating the child with physical injury, the major differentiation is the distinguishing of injuries that are abusive or inflicted from those that are accidental. The physician should be suspicious of changing histories, histories that are inconsistent with the injuries sustained, and histories that do not match the developmental capabilities of the child. Unwitnessed injuries in young children, particularly preambulatory infants, should also be suspect.

Bruises, burns, and fractures may be abusive or accidental. Normal ambulatory children commonly sustain bruises over bony prominences, such as the forehead, elbows, and shins, with unintentional, accidental trauma. Bruises over soft areas (eg, cheeks, pinnae of the ear) and on protected areas (eg, inner thighs, neck) are more suggestive of inflicted trauma. Injuries to the oral mucosa may result from efforts at forced feeding or occlusion of the mouth in an effort to silence crying. Retinal hemorrhages in infants most often result from abusive head trauma, such as shaking. They may also be the result of other medical conditions that usually can be discerned from the history and physical examination and by consultation with an ophthalmologist. Ideally, a pediatric ophthalmologist performs indirect retinal examination of dilated eyes within 24 hours of the patient's admission (Box 144.2).

Box 144.2. Causes of Mild Retinal Hemorrhage

- Abusive head trauma
- Unintentional head trauma
- Birth trauma
- Retinopathy of prematurity
- Blood dyscrasia
- Leukemia/lymphoma
- Meningitis/sepsis
- Extracorporeal membrane oxygenation
- Hyponatremia or hypernatremia
- Vasculitis
- Papilledema
- Hypertension
- Cytomegalovirus retinitis
- High-altitude illness
- Carbon monoxide toxicity
- Osteogenesis imperfecta
- Glutaricaciduria

Children may be intentionally burned by being immersed in hot water or having hot objects, such as irons or cigarettes, held against them. The child who is immersed in hot water develops circumferential burns that may envelop an entire extremity. Such a burn is usually in a glove or stocking pattern or in a doughnut pattern on the buttocks. These burns are distinct from splash or spill burns, which take on an irregular drip pattern. In distinguishing inflicted from accidental burns, a scene investigation is often helpful to measure the water temperature in the home water heater and determine the length of time required to reach that temperature in the location of the alleged incident. Families should be advised to set their water heaters to 120°F to prevent accidental scald injuries.

Long bone fracture, especially of the humerus and femur, are suspect, particularly in the preverbal or preambulatory child. Certain fractures, such as classic metaphyseal lesions as well as fractures of the rib, sternum, and scapula, are strongly suggestive of inflicted trauma.

Numerous medical conditions may mimic abuse. Bullous impetigo may resemble burns. A coagulopathy may result in multiple bruises. Leukemia, thrombocytopenia, and aplastic anemia are also associated with bruising. Osteogenesis imperfecta or rickets may result in multiple fractures. Bone cysts and osteoporosis caused by inactivity from multiple causes (eg, cerebral palsy, paralysis, meningomyelocele) may predispose to the development of pathologic fracture.

Evaluation

The child who presents with injuries requires evaluation with a careful history and complete physical examination. The infant with altered mental status, apnea, or seizures should be evaluated in a similar manner because these symptoms may be secondary to intracranial injury.

History

The history should focus on an explanation for the medical findings (Box 144.3) and, in infants and toddlers, a thorough developmental history should be included. The child should be interviewed alone if

Box 144.3. What to Ask

Physical Abuse

- What caused the injury?
- Was the child healthy until the injury occurred?
- Has the child sustained similar injuries in the past?
- Is the family history positive for any conditions that would account for easy bruising or fragility of the bones (eg, von Willebrand disease, osteogenesis imperfecta)?
- Is the child developmentally normal? What are the child's motor skills?
- Who was with the child when the injury occurred?
- What was done immediately after the injury? Was medical care sought?

of an appropriate age. The physician should determine if other risk factors, such as domestic violence or substance abuse, are present.

Physical Examination

A child's state of hygiene and growth parameters should be noted, and the physical examination should be comprehensive. The location, color, and size of bruises, abrasions, lacerations, or other skin trauma should be recorded. Dating of bruises cannot be done because the degradation rate of hemoglobin, and therefore the rate of color change, varies according to the depth and extent of the bruise and by the child's health and nutritional status. Large blue-gray spots, which occur commonly on the back and buttocks in darker-skinned children, are termed *mongolian spots* or *congenital dermal melanocytosis.* These should not be mistaken for bruises.

The physician should also note any skin findings that resemble characteristic patterns of inflicted skin trauma, such as slap marks to the face or gag marks around the mouth. Pinch marks can also be seen on the genitalia of a toddler undergoing toilet training. Belts, cords, and blunt objects may leave patterned marks on the skin after a child is hit with the object. Bite marks are composed of indentations, bruises, or breaks in the skin that reflect the configuration of teeth that is unique to the perpetrator (Figure 144.1). Inflicted burns may also assume a characteristic pattern depending on the mechanism of injury (Figure 144.2).

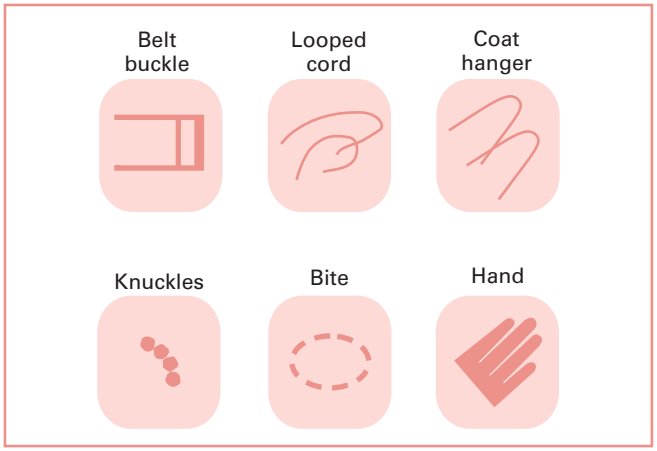

Figure 144.1. Patterned bruises associated with inflicted trauma.

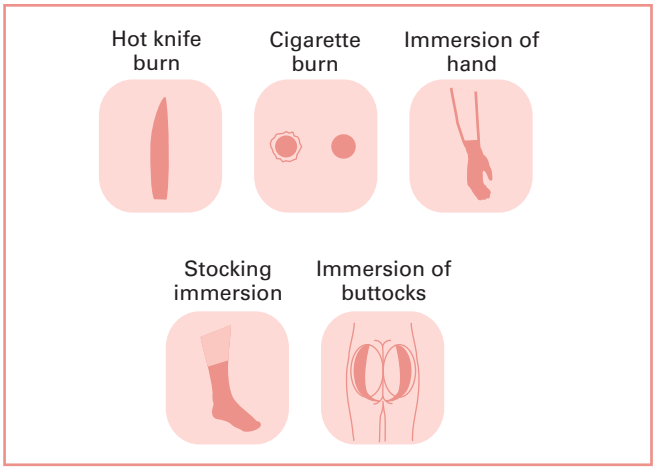

Figure 144.2. Patterned burns associated with inflicted trauma.

The extremities, skull, and rib cage should be carefully examined to detect the presence of skeletal trauma. Findings such as decreased range of motion, tenderness, swelling, redness, or bruising may be associated with an underlying bone fracture. These findings are not always present, however, particularly if the fracture is in its healing stages.

An infant with head or abdominal injury may exhibit no external signs of trauma. Infants and young children with head injury may have seizures, apnea, vomiting, increased crying, or altered mental status, often with no explanation concerning the etiology. The retina should be evaluated for hemorrhages in these children. The child with abdominal injury may present in shock or with symptoms such as vomiting, abdominal pain, or distention. Additionally, the child may have a rigid abdomen with guarding and decreased bowel sounds. Inflicted abdominal injuries may include hematomas of the bowel wall, bowel perforations, or trauma to the liver, spleen, pancreas, or kidneys.

Laboratory Tests

The child who presents with bruises should undergo a hematologic assessment with a complete blood cell count and differential (including a platelet count), a prothrombin time, and a partial thromboplastin time. Cultures from lesions may help differentiate impetigo or ecthyma from burn injury.

The child who presents with fracture should undergo assessment with a chemistry panel (including blood urea nitrogen and creatinine) and calcium, phosphorus, and alkaline phosphatase levels.

The child with suspected abdominal trauma should undergo evaluation with a complete blood count, urinalysis, liver function studies, amylase, and lipase. These studies may demonstrate anemia secondary to hemorrhage, hematuria from renal injury, or elevated liver or pancreatic enzymes resulting from trauma to a solid or hollow viscus organ (see Chapter 76).

A urine toxicology study should be considered as part of the evaluation in the child who presents with altered level of consciousness.

Imaging Studies

The child younger than 2 years who is a suspected victim of physical abuse is at the highest risk for an inflicted skeletal fracture. For this reason, such patients should undergo a radiographic skeletal survey

to identify any acute or healing fractures. Bone scintigraphy is also useful in detecting occult fractures and may be useful in conjunction with the skeletal survey. Follow-up skeletal survey (excluding the skull radiograph) in 2 weeks can also be useful to assess for fractures that were not noted at the time the initial radiographs were obtained.

The child with suspected nonaccidental head trauma should undergo computed tomography (CT) and magnetic resonance imaging of the brain and spine.

Abdominal radiographs may demonstrate air-fluid levels from dysmotility, distended loops of bowel, or free air under the diaphragm. Abdominal and pelvic CT with intravenous contrast is indicated for the patient in whom liver enzymes are greater than 80 U/L in the setting of suspected abdominal trauma. Bowel or solid organ disruption or hemorrhage may be evident on CT.

Management

Treatment of the child who is a suspected victim of abuse focuses on medical stabilization, careful and thorough documentation of medical findings, and psychosocial investigation. Injuries should be managed as appropriate. The child with extensive internal injuries frequently requires admission to an intensive care unit. Consultation with appropriate surgical specialists in neurosurgery, orthopedics, or general surgery should be obtained.

The psychosocial assessment of the family often requires the expertise of a social worker. Further assessment may require an in-home evaluation, such as that conducted by law enforcement or child protective services. All US states and territories require that physicians who suspect child abuse report these suspicions to the appropriate agencies. The physician does not have to be certain that abuse occurred.

These agencies pursue the investigation and provide supportive family services as necessary. A child may be removed from the home and placed in foster care to ensure the child's safety. Cases of suspected abuse are usually assessed in dependency court to determine the safety of the child's environment, ability of the parent(s) or guardian(s) to care for the child, and in criminal court to assess the culpability of suspected perpetrators. The physician may be expected to offer testimony in such hearings.

Prognosis

The prognosis is variable. Some children succumb to inflicted injuries before coming to medical attention, and others sustain permanent neurologic damage. Even in cases in which the physical well-being of the child is ensured, often the child's mental and emotional well-being is significantly affected, requiring intensive and ongoing mental health care.

Recent longitudinal studies in adults have shown a link between adverse childhood experiences and health problems in adulthood (see Chapter 142).

Prevention

The physician should preemptively discuss with families those developmental stages with increased risk for parental frustration and subsequent child abuse, including infant colic, toddler potty training, and tantrums. Infant crying is the most common trigger for abusive head injury. The pediatrician may offer guidance in managing these difficult situations and should assess the coping skills of the parent(s)/guardian(s) with such behaviors when they arise. The pediatrician should also inquire about stressors particular to each family, such as unemployment, mental health issues, social isolation, and intimate partner violence. Support systems for the family should be identified and positive attributes praised.

CASE RESOLUTION

The case study is a classic case of abusive head trauma. The infant was left alone with an individual no prior experience caring for a young infant. The infant has evidence of increased intracranial pressure and may have traumatic axonal injury or intracranial hemorrhage. The infant is intubated, administered anticonvulsant agents, and admitted to a pediatric intensive care unit. Consultation with neurosurgery, ophthalmology, and social services is obtained. Appropriate imaging studies and skeletal surveys are performed when the infant is sufficiently stabilized, and the child is ultimately diagnosed with subdural hemorrhage, retinal hemorrhages, and rib fractures.

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CHAPTER 145

Sexual Abuse

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CASE STUDY

A 4-year-old girl is brought to the emergency department with the report of vaginal itching and discharge. Her past health has been good, and she has no medical problems. She lives with her biological parents and her 2-year-old brother.

On physical examination, the vital signs are normal and the child is well, except that the genital area is swollen and erythematous and a green vaginal discharge is present. The girl is interviewed briefly but denies that anyone has touched her. The mother states that she has never left her daughter unattended and is angered by the questions about possible sexual abuse.

Questions

1. What are the anogenital findings in prepubescent and postpubescent children who may have experienced sexual abuse?
2. What behavioral problems are common among children who have been sexually abused?
3. What are the pitfalls in disclosure interviews of children who have been sexually abused?
4. What is the significance of sexually transmitted infections in children who have been sexually abused?

Child sexual abuse is the involvement of children and adolescents in sexual activity that they cannot consent to because of their age and developmental level. An age disparity exists between the targets, who are younger, and the perpetrators, who are older. The intent of the abuse is the sexual gratification of the older individuals, and the abusive incident(s) may or may not include physical contact. Sexual abuse may include acts of oral, genital, or anal contact by or to a child and may involve acts such as exhibitionism or involvement in pornography. It is differentiated from "sexual play" by the difference in the developmental levels of the participants and the coerciveness of the behavior.

Sexual abuse has been recognized with increasing frequency since the 1980s, in part because medical knowledge about the anogenital anatomy in molested and nonmolested prepubescent children has expanded. Technical advances have altered the manner in which these children are evaluated. In particular, the colposcope, with its potential for magnification and photographic or video recorded documentation, has been valuable. Parental awareness and school-based programs have resulted in increased disclosures about abuse as well as a greater willingness on the part of adults to believe these disclosures.

Patient interviews are another key component of the assessment process that has been shaped by continued research in the field. Non-leading, open-ended questions are asked by interviewers as few times as possible, and when available, specialized forensic interviewers ask these questions.

Epidemiology

In 2015, an estimated 676,000 children were targets of child maltreatment in the United States, and just under 10% of these were targets of sexual abuse. Exact figures on the prevalence of child sexual abuse are not readily available because they depend on reports of a condition that may not come to medical attention for many years. Anonymous surveys indicate that approximately 20% to 25% of women and 10% to 15% of men have been sexually abused before reaching adulthood.

Targets of sexual abuse come from all socioeconomic and ethnic groups. Girls experience sexual abuse at a rate 5 times that of boys. Some investigators believe that the statistics for boys are falsely low because boys are generally reluctant to disclose their abuse. Men are more commonly the perpetrators than women, and at least 20% of perpetrators are adolescents. Frequently, the sexual abuse has been occurring for several years. Perpetrators are usually known by the targets, and recent national data showed that 37% of perpetrators were biological parents, 23% were nonbiological parents, and 40% were other individuals. The mean time from onset of abuse to disclosure is 3 years. Sometimes children are not ready to disclose but the abuse is discovered incidentally because the targets develop symptoms, such as vaginal discharge or functional symptoms.

Clinical Presentation

Most cases of child sexual abuse come to the attention of authorities after the child discloses the abuse. Associated physical or behavioral symptoms may or may not be present. Physical symptoms in the anogenital area may include bleeding, pain, swelling, dysuria, vaginal discharge, or difficulty passing stool. More often, however, children have no specific anogenital symptoms. Instead, they have nonspecific symptoms, such as headache or abdominal pain, or vague systemic symptoms, such as fatigue (Box 145.1).

Behavioral changes may also be noted as these children respond to the stress of being targeted and of their environments. These

Box 145.1. Diagnosis of Child Sexual Abuse

- Anogenital erythema
- Anogenital bleeding
- Genital discharge
- Anogenital scarring
- Behavioral symptoms (eg, encopresis, enuresis)
- Disclosure of abuse
- Somatic symptoms (eg, abdominal pain, headache)
- Sexually transmitted infections
- Sexualized behavior
- Pregnancy (adolescents)
- Delinquency, promiscuity (adolescents)

changes may include sleep disturbances, hyperactivity, enuresis, encopresis, decreased appetite, and depression. The sexually abused adolescent may manifest school failure, delinquency, and suicide attempts. A child may also respond with sexual behavior or sexual knowledge that is considered inappropriate or excessive for age.

Psychophysiology

Children are subjected to sexual abuse after becoming entrapped. They may be enticed with promises of rewards or presents or may be made to feel special or grown up by being allowed to engage in adult behavior. Some children do not regard the sexual experiences as threatening but rather as a means by which they can obtain the love they crave. Only when they grow older do they realize that these sexual relationships were not normal or appropriate.

Other children are coerced into sexual activity with threats of physical harm. Once they have acquiesced, they are maintained in the relationship with threats of reprisal if they disclose the abuse. Children feel guilty and responsible for what has happened. This sense of responsibility for family disruption is often perpetuated by the legal system, which may remove the children from their families or place the offending family member in custody.

Finally, some children enter into sexual relationships out of curiosity. They too become entrapped, particularly because they were initially willing to participate.

As a child reacts to an abusive experience, it is common to feel a need for secrecy. As a result, disclosures of abuse are often delayed, and when they do occur, the child often provides the information incrementally over time. A child may also recant disclosures about abuse; such recantations are not considered to reliably indicate that the abuse did not occur.

Differential Diagnosis

Several medical conditions involving the anogenital area may be mistaken for acute or chronic changes resulting from sexual abuse (Box 145.2).

A child may sustain accidental blunt or penetrating injury to the genital area. The most common of these are straddle injuries that occur from falls with impact to the genital area. Pain and bleeding

Box 145.2. Conditions Mistaken for Sexual Abuse

Genital

- Accidental trauma
- Lichen sclerosus et atrophicus
- Urethral prolapse
- Labial adhesions
- Congenital malformations
- Hemangioma

Anal

- Inflammatory bowel disease
- Hemorrhoids
- Anal abscess associated with neutropenia
- Perirectal abscess
- Perianal streptococcal infection

are the most common symptoms with these injuries, and external genital structures, such as the labia majora, labia minora, and periurethral areas, are typically affected. The hymen is unaffected.

Genital bleeding is also a frequent symptom in girls with urethral prolapse, a condition that is reported most often in prepubescent black girls between 4 and 8 years of age. These girls have a protuberant mass extruding from the urethra. The condition is of uncertain etiology, but it is not related to abuse.

Lichen sclerosus et atrophicus, which is a less common dermatologic condition that can also be confused with the sequelae of sexual abuse, typically is characterized by atrophic, hypopigmented skin in a figure-of-8 configuration in the anogenital area with associated macules, papules, and hemorrhagic blisters. The skin changes may be misinterpreted as scarring from prior abuse and because the atrophic skin is easily traumatized, findings may also be confused with recent abuse. One factor that may differentiate this condition from injuries related to sexual abuse is that the hymen is unaffected in lichen sclerosus et atrophicus.

Labial adhesions occur most commonly in toddlers and may be confused with scarring from prior sexual abuse. The adhesions occur as the result of inflammation in the genital area of a prepubertal (ie, hypoestrogenic) female. Such inflammation has multiple causes, including poor hygiene, recurrent vulvovaginitis, and trauma. The presence of labial adhesions is not a specific indicator of past sexual abuse.

Congenital malformations may also affect the anogenital area. Failure of midline fusion along the median raphe can have the appearance of denuded skin and may be confused with an abrasion or superficial laceration of the area. This failure of fusion is a congenital finding, however, and no bleeding is evident, as would occur with a traumatic injury. Other congenital malformations include hemangiomas that may bleed and be mistaken for traumatized tissue. These hemangiomas are most often noted in infants and children younger than 2 to 3 years, and they usually regress with time.

Medical conditions may also affect the perianal area and may be mistaken for abuse. Crohn disease may result in fissures, fistulas, perirectal abscesses, or tags. Generally, Crohn disease affects older children and produces other symptoms, such as fever, weight loss, and problems passing stool, or extraintestinal symptomatology. Perirectal abscesses may occur in patients with neutropenia, sometimes as the presenting symptom of leukemia. Hemorrhoids occur rarely in children, and their presence should raise concern for intra-abdominal venous congestion.

Conditions causing vaginal discharge may be related to sexual abuse, particularly if they are secondary to sexually transmitted infections (STIs), such as gonorrhea or chlamydia infection (Box 145.3). Other agents, including *Candida*, shigella, and group A β-hemolytic streptococci, may produce similar symptoms, yet not be sexually acquired. The streptococci may produce a painful erythematous rash in the perianal area, which is frequently misdiagnosed as secondary to trauma or sexual abuse.

Evaluation

The extent and urgency of the evaluation is in part dependent on whether the allegations involve an acute abusive episode or an episode that occurred in the past. An acute abusive episode (occurring within the previous 72 hours) warrants an immediate assessment for evidence that may otherwise be lost within hours.

History

When a child presents with a physical finding, statement, or behavior that raises the concern of possible sexual abuse, it is important for the examiner to ask carefully thought out, non-leading questions to determine whether the level of suspicion has been reached such that the examiner is mandated to report the concern to a child protective services agency. Beyond that, an attempt should be made to minimize the number of times the child is questioned about the abuse-related incidents. It is also important to establish sufficient medical history to address any pressing clinical issues. Such a history should include a review of systems, menstrual history, sexual activity history, past incidents of abuse, and any prior genital trauma or medical procedures of the anogenital area. A psychosocial history should also be obtained, because behavioral problems, depression, anxiety, suicidality, homicidality, and other issues requiring mental health expertise are common in children who have been sexually abused (Box 145.4).

Because most targets of sexual abuse have a normal physical examination, the history is often of primary importance. As a result, the child must also be interviewed by someone with professional expertise in the areas of interviewing and child sexual abuse. This individual may be a physician or a social worker, psychologist, rape counselor, or detective or district attorney assigned to the abused child unit. The interview should be structured to include open-ended questions, such as, "Can you tell me what happened?" (Box 145.5). Interview tools, such as drawings, may be used but are best left to experts with experience in these controversial modalities. Statements that children make should be recorded in the medical record as close to verbatim as possible.

Physical Examination

It is helpful for the examiner to be familiar with the normal anogenital anatomy of prepubescent children. The anatomy of boys remains constant throughout childhood, except for the increase in size of the penis and testes and the appearance of pubic hair during adolescence. Figure 145.1 shows the normal anogenital anatomy of prepubescent girls, which changes from infancy through adolescence. All girls are born with a hymen, which is thick and full and covers the hymenal orifice in newborns. As maternal hormones regress, the hymen becomes thinner and more

Box 145.4. Problems Reported in Children Who Have Been Sexually Abused

- Enuresis
- Encopresis
- Sexualized behavior
- Pseudomaturity
- Vaginal discharge
- Sleep disturbances
- Suicide
- School failure
- Delinquency (adolescents)
- Promiscuity (adolescents)

Box 145.3. Conditions Associated With Vaginal Discharge

- Gonorrhea
- Chlamydia
- *Trichomonas*
- Bacterial vaginosis
- Candidiasis
- Shigellosis
- Group A β-hemolytic streptococcus infection
- Vaginal foreign body

Box 145.5. What to Ask

Child Sexual Abuse

- Can you tell me what happened?
- Has anything like this happened before? If so, what happened the first time?
- Who did this to you?
- Has anyone else done this to you?
- How often has this happened?
- Where were other people (eg, your mother) when this happened?
- Did you tell anyone? Who? What did they do?

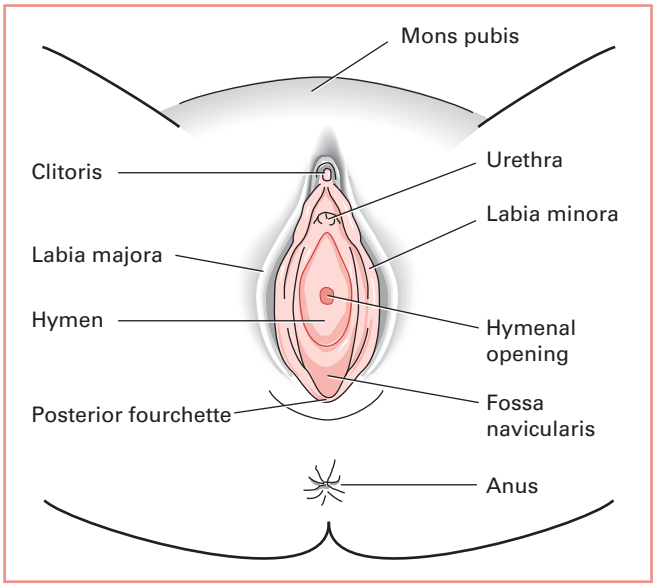

Figure 145.1. Normal anogenital anatomy of the prepubescent girl.

translucent, frequently taking on an annular or crescentic configuration. When puberty begins, the hymen once again becomes thickened, scalloped, and full. Careful examination of the hymen may involve positioning a child in not only the supine frog-leg position but also the prone knee-chest position (Figure 145.2). For a variety of reasons, often no genital abnormalities are noted on examination of targets of sexual abuse. Penetration of the hymen in the postpubertal adolescent may result in stretching without tearing of the tissue, and in the prepubescent child, hymenal transection may heal with little residual evidence of the trauma. Many types of abuse (eg, orogenital contact, fondling) commonly leave no visible findings. The medical examiner must therefore realize that a normal anogenital examination does not preclude sexual abuse.

In cases of acute molestation, evidence of injury may be readily apparent, particularly if the examination is performed with the assistance of magnification, such as colposcopy. Injuries that may be noted include ecchymoses, petechiae, active bleeding, abrasions, and lacerations. Those caused by penile penetration commonly involve the hymen in the 6-o'clock position and the area of the posterior fourchette (Figure 145.1).

The evaluation of the child who has been molested in the past or on a chronic basis is more problematic. Many injuries heal with little residual scarring. Scarring that does occur may appear as a notch or concavity in the contour of the hymenal edge. The pattern of blood vessels may also be interrupted, and areas of increased or decreased vascularity may be apparent. Sometimes a marked reduction in the amount of hymenal tissue is present in an area of prior trauma.

Male genitalia are less often injured by sexual abuse. More often the injuries seen in prepubescent boys, as well as in some girls, involve changes in the perianal area. The incidence of these changes in all children who have been sodomized is unknown but is believed to be low. When changes do occur, they may appear as scars, tags, or irregularities in perianal rugae and anal tone.

Laboratory Tests

When the molestation has occurred within 72 hours of the examination and the mechanism of injury could have resulted in deposition of body fluids on the child, forensic evidence should be collected as required by law enforcement. For adolescents, DNA evidence may be retrieved up to 120 hours after the assault. This evidence usually involves samples of vaginal washings and dried secretions, which are evaluated for the presence of DNA in an effort to identify the perpetrator. Clothing that was worn at the time of the assault should also be submitted, because it is frequently positive for DNA evidence. Forensic packages, which are referred to as "rape kits" and are distributed by law enforcement agencies, have specific instructions concerning the appropriate collection of samples. Completion of the rape kit is best performed by a nurse or physician who has undergone specialized training in the process.

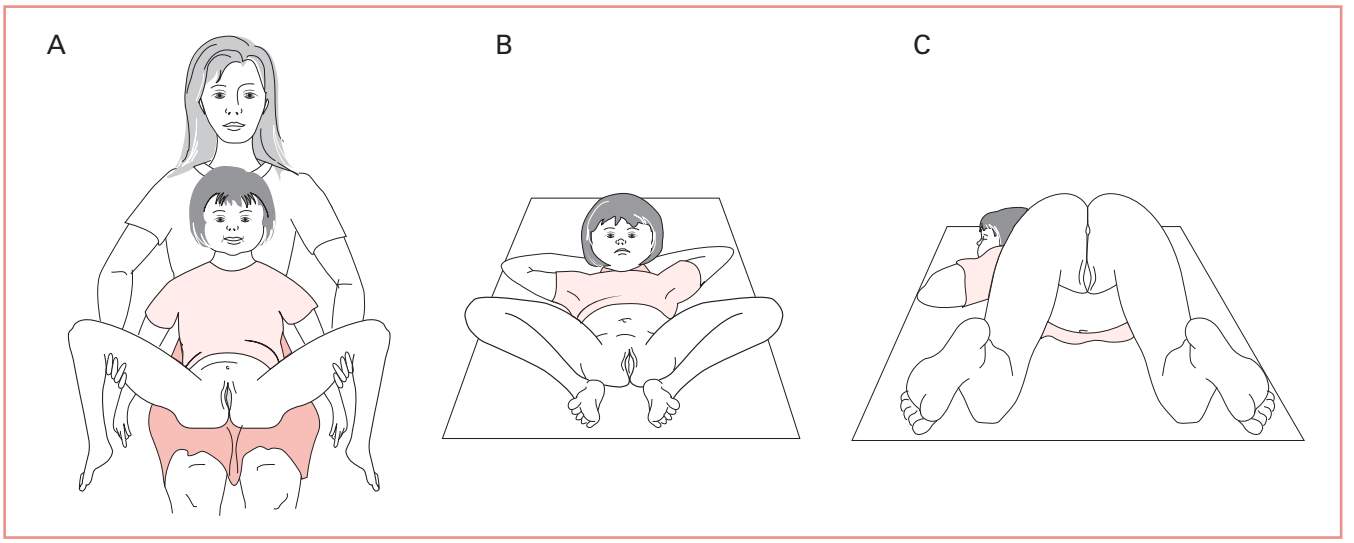

Figure 145.2. Various positions for an anogenital examination in a prepubescent girl. A, Seated on the mother's lap. B, Supine, frog-leg position. C, Prone, knee-chest position.

Studies indicate that 1% to 5% of children who were sexually abused acquire an STI as a result of the abuse. Because of this, testing for STIs is typically targeted toward any child with a history of genital, oral, or anal penetration; a sibling with an STI; an assailant with a history of an infection; or a child, sibling, or assailant with signs or symptoms of an STI. If testing is indicated, cultures should be obtained from the involved body areas (eg, vagina or urethra, rectum, throat). At a minimum, a child with genital discharge should be evaluated for *Neisseria gonorrhoeae, Chlamydia trachomatis*, and *Trichomonas vaginalis*. The presence of these infections in a prepubertal child, in the absence of perinatal transmission, is indicative of prior close genital contact. Most frequently this is the result of sexual abuse. It is impossible to determine the etiology of vaginal discharge based only on its clinical characteristics.

All tests for STIs in prepubertal children should be evaluated in a reliable laboratory because of the legal implications of venereal infections in young children. Culture is considered the standard for diagnosing gonorrhea and chlamydia in this setting because of its high specificity. Newer nucleic acid amplification tests (NAATs) may have higher sensitivity in some settings, and although they may be used in the evaluation for gonorrhea and chlamydia in the pubertal or prepubertal child, they should not be used as the sole method of evaluation. A positive NAAT should be confirmed by culture or by a second nucleic acid test targeting a different DNA sequence. Many experienced laboratories have protocols for automatic confirmatory testing of a positive NAAT in a prepubertal child, with testing for a second DNA sequence. Culture rather than NAAT should be used to test for gonorrhea and chlamydia in extragenital sites.

Testing for HIV, syphilis, hepatitis B, and hepatitis C should be performed if signs or symptoms of the diagnosis are present, another STI is detected, the perpetrator is known to be infected, or the patient or family specifically request the testing. Genital warts can be diagnosed clinically, and any lesions suspicious for human herpesvirus 1 or 2 should be cultured and typed. Although culture remains the standard for diagnosing human herpesvirus infection, because of the low sensitivity of culture, polymerase chain reaction may also be performed on the lesion. Serologies for human herpesvirus type-specific glycoprotein G antigens may be helpful if culture and polymerase chain reaction are not available. Pregnancy testing should be considered in any postpubertal girl.

Table 145.1. Management of Sexually Transmitted Infections in Children

Infection	*Medication*	*Dose*
Neisseria gonorrhoeae	Ceftriaxone sodium	250 mg IM × 1 dose (weight ≥45 kg)
	OR	
	Cefixime	400 mg PO × 1 dose (weight ≥45 kg)
	Ceftriaxone sodium	25–50 mg/kg IM × 1 dose (maximum: 125 mg) (weight <45 kg)
Chlamydia	Erythromycin	50 mg/kg/day divided qid × 14 days (maximum: 2 g/day) (weight <45 kg)
	OR	
	Azithromycin	60 mg/kg PO × 1 dose (maximum: 1 g) (weight <45 kg)
	Doxycycline	100 mg PO bid × 7 days (age >8 years, weight ≥45 kg)
	OR	
	Azithromycin	1 g PO × 1 dose (age >8 years, weight ≥45 kg)
Genital herpes	Acyclovir	400 mg PO tid × 7–10 days (weight ≥45 kg)
		80 mg/kg/day divided qid × 7–10 days (maximum: 3.2 g/day) (weight <45 kg)
Trichomonas	Metronidazole	45 mg/kg/day divided tid × 7 days (maximum: 2 g/day) (weight <45 kg)
		2 g PO × 1 dose (weight ≥45 kg)
Bacterial vaginosis	Metronidazole	15–25 mg/kg/day divided tid × 7 days (maximum: 2 g/day) (weight <45 kg)
		500 mg PO bid × 7 days (weight ≥45 kg)
Syphilis	Penicillin G benzathine	50,000 U/kg, single IM dose (maximum: 2.4 million U)

Abbreviations: bid, twice a day; IM, intramuscularly; PO, orally; qid, 4 times a day; tid, 3 times a day.

Management

The management of children who have been sexually abused has 3 major components. First, any medical problem sustained as a result of the abuse, such as traumatic injuries, must be addressed. Additionally, STIs should be managed (Table 145.1). See Chapter 60 for a more extensive discussion of STIs in adolescents. The adolescent who has been the target of an acute assault should be offered pregnancy counseling, STI prophylaxis, and emergency contraception as medically indicated. Second, the emotional well-being of the patient must be ensured. In cases of acute assault, crisis intervention is mandatory. If a child has been the target of chronic or prior sexual abuse, referral to appropriate counseling services should be done. Third, the physician must report the incident of sexual assault or abuse to the appropriate agencies, as mandated by the laws of the locality in which the physician practices. The physician may be required to testify in court about particular findings and whether abuse occurred. Testifying may be intimidating. It is helpful for the physician to review the medical records in advance of the appearance in court and discuss this information with the attorney who issues the subpoena to the physician.

Prognosis

Several factors influence the prognosis in cases of child sexual abuse, including the relationship of the perpetrator to the child, chronicity of the abuse, support after the disclosure, and preexisting psychosocial conditions. Typically, physical injuries are nonexistent or minor, and healing occurs with minimal residual evidence. In most cases, psychological counseling is indicated. Such counseling is beneficial,

and emotional recovery is not only possible but likely to occur in a supportive environment.

Studies of adverse childhood experiences have shown that child sexual abuse is associated with an increased risk of medical, psychological, and social problems in adulthood (see Chapter 142).

CASE RESOLUTION

The mother claims that no one has access to her child; however, the girl's symptoms strongly suggest an infection with *Neisseria gonorrhoeae.* Secrecy about abuse is quite common. The child and mother should be interviewed by a skilled person. Cultures for gonorrhea should be carefully collected and sent to the most reliable laboratory. Antibiotic therapy may be initiated if the child is symptomatic. The case may be referred immediately to social services and law enforcement agencies if a disclosure is made. Alternatively, if the child denies the abuse, the referral may be deferred pending laboratory confirmation of the diagnosis.

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CHAPTER 146

Failure to Thrive

Carol D. Berkowitz, MD, FAAP

CASE STUDY

A 2-year-old girl is brought to the office because of her small size. She was born at term but weighed only 2,200 g (4.9 lb [<5th percentile]) and measured 43 cm (16.9 in [<5th percentile]). The mother is a 30-year-old gravida 5, para 4, aborta 1 who smoked during pregnancy but denies using alcohol or drugs. She received prenatal care for only 2 weeks just prior to delivery, and she claims to have felt well.

The child's physical health has been good. She is reported to be normal developmentally but speaks only 4 to 5 single words. She has not yet started toilet training.

The family history is negative for medical problems, including allergies, diabetes, and cardiac and renal disease. The mother is 5 feet (152 cm) tall, and the father is 5 feet, 4 inches (163 cm) tall. The girl has 3 siblings, aged 5 years, 4 years, and 3 years, all of whom are normal. The father is no longer in the household. The mother is not employed outside the home, and she receives public assistance. She states that frequently there is not enough food in the home, although she receives food stamps (ie, Supplemental Nutrition Assistance Program).

On physical examination, the girl is below the fifth percentile in height and weight. Although she is quite active, she does not use any understandable words. The remainder of the examination is normal.

Questions

1. What are the key prenatal factors that affect the growth of children?
2. How can caloric adequacy of a diet be assessed?
3. How do parental measurements affect their children's stature?
4. What are the behavioral characteristics of the infant with environmental failure to thrive?
5. What are some strategies to increase caloric intake of infants and children?
6. What, if any, laboratory studies should be routinely obtained when evaluating a child for failure to thrive?

Failure to thrive (FTT) is a condition in which a child is not growing and developing at an appropriate rate for their age. The term is most often applied to infants and toddlers younger than 3 years. Failure to thrive is not a disease or even a diagnosis but represents a sign that a child's size or rate of growth is below the expected. The term FTT first appeared in the pediatric literature in 1933 and was used for children whose growth impairment related to a suboptimal environment. Before 1933, the condition was referred to as "cease to thrive." The terms "growth deficiency," "growth impairment," "undernutrition," and "inadequate growth" are sometimes used interchangeably.

Historically, FTT has been divided into 2 distinct categories—organic and nonorganic. In *organic FTT*, an underlying medical problem, such as cystic fibrosis or congenital heart disease (CHD), is believed to contribute to the failure to grow at an appropriate rate. In *nonorganic FTT*, also referred to as *environmental deprivation*, inadequate growth is attributed to lack of nourishment and a non-nurturing home environment. Some physicians use the term FTT exclusively to mean environmentally related growth impairment. It is important to recognize that many children with growth problems have organic as well as environmental components, a condition sometimes referred to as *multifactorial FTT* or *mixed FTT*.

The diagnosis of FTT is entertained when the growth parameters of children as plotted on a standardized curve are below the fifth percentile in height and/or weight. Children who are above the fifth percentile may also be diagnosed with FTT if the rate of growth has decelerated and 2 major percentiles (eg, decreased from the 75th percentile down to the 10th percentile) have been crossed within 6 months (Box 146.1). Studies have shown, however, that between birth and 6 months of age, approximately 40% of healthy infants cross 2 major percentiles on the weight-for-age curve (up or down), as do up to 15% of children between 6 and 24 months of age. Similar trends are noted for length. The physician should, however, carefully track these infants to be certain that such changes are related to the child's genetic disposition and not an environmental or medical problem.

The challenge for the physician caring for the child with FTT is to determine the etiology of the problem, which may not be readily apparent. Nonspecific, nondirected laboratory tests are not helpful because their yield is low and their cost is high. The evaluation of the small, underweight child requires a careful history and physical examination as well as an assessment of caregiver-infant interactions. A home visit helps because it permits evaluation of the caregiver-infant relationship in a more natural setting and an assessment of the family's economic and food resources.

Box 146.1. Diagnosis of Failure to Thrive

- Weight <5th percentile
- Height <5th percentile
- Weight for height <5th percentile
- Rate of growth lower than expected
- Deceleration of the growth rate
- Parental concern about the child's eating
- Delayed developmental milestones
- Disturbed interactional skills

Epidemiology

The prevalence of FTT varies in different segments of the population. Poverty puts children at risk for undernutrition, and 12% of Medicaid recipients are below the third percentile in weight. Child neglect can result in FTT but is not a necessary component; 60% to 70% of cases of child abuse are reported for child neglect. Several other factors may contribute to variations in growth. All of these are not the result of a pathologic process but may reflect variations in individual genetic potential.

Environmentally related FTT may occur in different family settings. In some families, an acute depressive episode in the mother is the key component (see Chapter 24). Family living conditions are good, and the educational background of the mother is adequate. The depressive episode may be related to a loss that occurred during the pregnancy or shortly after delivery or to perinatal mood and anxiety disorders, a group of mental health conditions associated with pregnancy and delivery and manifested after birth. In these cases, the mother is too depressed, withdrawn, or preoccupied to interact effectively with her children. The condition may affect 25% to 30% of mothers, and the prevalence is influenced by many factors, including poverty, race, and access to health care. In other families, financial resources are marginal. The mother may be chronically depressed, and the father may be involved in alcohol or substance abuse. Domestic violence is a frequent occurrence (see Chapter 142). Spacing between children is fewer than 18 months, and the number of children is often the same as the age of the oldest child. The mother is too overwhelmed to meet the needs of all the children. A third type of family also involves a mother with depression and who has experienced losses, usually of a chronic nature. Her financial and educational backgrounds are adequate, but she views 1 of her children (the child who now presents with FTT) as bad or evil and the source of all her problems. As a result, an individual child is singled out, and the neglect is intentional.

Clinical Presentation

The child with FTT presents with low weight, short stature, poor appetite, or failure to gain weight or grow taller. Sometimes a parent or guardian may express concern; at other times, a teacher may detect a child's growth problems. Some children with FTT are diagnosed during a health maintenance visit or during evaluation for another medical problem, such as a febrile illness. Following a child longitudinally will give the physician a better sense of the child's growth pattern and a clue to the etiology of observed growth impairments. When nutrition is suboptimal, weight tends to decrease first, followed by length and, ultimately, head circumference.

Pathophysiology

The common pathway for the development of FTT, regardless of etiology, is insufficient calories to meet the nutritional needs of the child (Box 146.2). Caloric intake may be inadequate for several reasons. Some factors are societal, specifically poverty and inadequate access to food. Other factors may involve increased caloric needs. Certain chronic conditions are characterized by increased caloric expenditure (eg, some forms of chronic lung disease) or increased loss of ingested food (eg, diarrhea, malabsorption syndromes).

In environmentally related FTT, a disturbed caregiver-infant relationship contributes to reduced caloric intake and associated gastrointestinal symptoms (ie, vomiting). Although various disturbances in mother-FTT infant dyads have been described, maternal depression is the most common maternal feature noted in environmentally related FTT. Infants withdraw after unsuccessful attempts to interact with nonresponsive mothers, and infants become apathetic and disinterested in food. Alternatively, overactive mothers, some of whom have an untreated bipolar (eg, manic-depressive) disorder, are out of synchrony with their infants. The infants become agitated, especially during feedings, and cannot feed and frequently vomit. These infants, who may interact with persons other than their mothers, usually do well in other environments or when their mothers receive appropriate therapy.

Older children with long-standing environmental deprivation have disturbed hypothalamic-pituitary functioning. The etiology of this dysfunction is uncertain but has been attributed to sleep disturbances with an effect on levels of growth hormone.

Some children develop FTT as a result of a feeding disorder. The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition

Box 146.2. Factors Affecting Calories Available for Growth

Insufficient Intake

- Poverty
- Inadequate access to food
- Improper formula preparation
- Eating difficulties
- Vomiting

Increased Loss

- Malabsorption

Increased Needs

- Congenital heart disease
- Chronic lung disease

(*DSM-5*) includes a new diagnostic category, avoidant/restrictive food intake disorder (ARFID), which includes individuals of all ages with reduced food intake without necessarily having body image concerns. The *DSM-5* describes 3 examples of ARFID: sensory sensitivity (includes children with texture aversions); low appetite or lack of interest in food (ie, picky eater); and avoidance of specific foods because of a prior traumatic experience (eg, choked while eating meat.)

Differential Diagnosis

The growth of the child with FTT may be impaired in weight, height, head circumference, or any combination of growth parameters. If weight is the only abnormal parameter, inadequate caloric intake, excess caloric loss, or increased caloric expenditure is likely the major problem. If height is reduced and weight is appropriate or high for height, the diagnosis may be short stature rather than FTT. Small head circumference in the setting of low growth parameters is suggestive of a central nervous system basis for the growth delay. It is important to determine if the child's skills are developmentally appropriate when determining the etiology of FTT. Affect and interactional skills should be noted as well. Environmentally deprived infants are apathetic and noninteractive. They appear hypertonic and may be diagnosed with cerebral palsy or have features suggestive of infantile autism spectrum disorder; however, their symptoms resolve with a change in surroundings.

The most common causes of short stature include familial short stature and constitutional delay. The child with familial short stature is small because the parents are short. The bone age of the child with familial short stature is the same as the child's chronologic age. Except for a deceleration in growth, which usually occurs between ages 6 and 18 months, the child with constitutional delay appears healthy. Unlike the child with familial short stature, the child with constitutional delay has a delayed bone age that is comparable to the child's height age (ie, the age when height is at the 50th percentile), however. In the child with familial short stature or constitutional delay, growth parameters at birth are usually normal.

The child with low growth parameters at birth may have been born preterm or have experienced intrauterine growth restriction (IUGR). Most studies support the notion that well preterm infants exhibit catch-up growth (head circumference by 18 months, weight by 24 months, and height by 40 months). The ill preterm infant may not demonstrate such catch-up growth because of increased caloric needs related to residual medical problems (eg, chronic lung disease) or impaired nutritional intake resulting from certain conditions (eg, cerebral palsy with discoordinated swallowing). Overall, 15% of infants who are classified as IUGR or small for gestational age do not exhibit catch-up growth. Significant evidence now exists that IUGR may be associated with insulin resistance and subsequent propensity to obesity and metabolic syndrome. Disturbances in leptin, ghrelin, and adiponectin have also been described. This has significant implications for the management of these infants vis-à-vis their nutritional intake. It is postulated that some individuals are "programmed" to be slighter and smaller, and nutritional interventions to achieve a more average weight have deleterious effects later in life.

The child who is small for gestational age may have experienced any of several in utero insults that affect postnatal growth, including exposure to cigarettes, alcohol, and illicit drugs. Additionally, maternal infection with such diseases as rubella may result in a congenital infection in the infant with subsequent growth impairment.

Several other conditions may result in disturbed growth, including endocrine disorders, skeletal dysplasia, food allergies, and malabsorption. These conditions occur less frequently and are usually more readily apparent as children undergo evaluation for the growth problem.

Evaluation

History

Careful questioning about certain specific topics provides clues to diagnosis in approximately 95% of cases. The physician should learn about the pregnancy and delivery, the family history (including parental heights), the child's medical and dietary history, and the child's feeding pattern.

It is important to obtain an in-depth history of the pregnancy and delivery (Box 146.3). The infant's birth weight and gestational age are key pieces of information. Low birth weight is said to account

Box 146.3. What to Ask

Pregnancy and Delivery

- Was the pregnancy planned?
- How did the mother feel when she learned that she was pregnant?
- Was prenatal care obtained?
- How many times has the mother been pregnant?
- Is there a history of abortions (spontaneous or therapeutic)?
- How much alcohol did the mother drink during the pregnancy, if at all?
- How much did the mother smoke during the pregnancy, if at all?
- How much did the mother use drugs (prescribed or illicit) during the pregnancy, if at all? If drugs were used, which ones?
- Did the mother take any medications during the pregnancy?
- Did the mother have any rashes or illnesses during the pregnancy?
- How did the birth of the baby affect the family structure?
- Has the mother felt depressed or anxious?
- Has the mother felt little interest or pleasure in doing things?
- Was the baby term or preterm?
- How much did the infant weigh at birth?

Medical, Feeding, and Family History

- Is the child's growth rate normal or slow?
- Has the child had any previous illnesses (eg, gastroenteritis, recurrent pneumonia)?
- Does the child tire easily?
- Is the child taking any medications, and if so, for how long?
- Is the child a picky eater?
- Is the child hesitant to try new foods?
- What does the child eat over the course of a given day?
- How tall are the parents?
- Do any medical problems run in the family?

for 20% to 40% of short stature in children from low-income families. It is helpful to confirm that neonatal screening for genetic and metabolic diseases was normal. Recurrent spontaneous abortions suggest that a mother may have an underlying problem, such as a balanced chromosomal translocation that results in fetal wastage. The mother who has experienced repeated losses may have difficulty bonding with subsequent babies. The physician should determine whether the mother used cigarettes, alcohol, or drugs during the pregnancy by asking the mother questions beginning with the phrase, "How much?" Any medications taken by the mother may affect the subsequent growth of the infant.

A review of the child's medical history may also provide a clue to the etiology of FTT (Box 146.3). It is essential that the physician obtain as many of the previous growth parameters as possible to determine whether the child is small but growing at a normal rate or if the rate of growth is slow or has fallen off. Previous illnesses should be assessed, because these events may interrupt growth temporarily. Certain symptoms may be indicative of underlying organic disorders, and recurrent infections raise the possibility of a congenital or acquired immune disorder, including infection with HIV. A history of easy fatigability may be a clue to CHD. Although most children with CHD grow normally, growth problems may occur with congestive heart failure, some forms of cyanotic heart disease, and complex atrial septal defects, especially if associated with pulmonary hypertension. A history of diarrhea may be suggestive of an underlying gastrointestinal disorder with subsequent malabsorption. The child with urinary incontinence may have renal disease that interferes with growth. The presence of seizures may be a sign of a central nervous system problem that makes it difficult to obtain adequate nutrition. Some children with seizures are heavily medicated and are too sleepy to eat.

It is important to query whether the child is on any medications. The chronic use of some medications, such as corticosteroids and certain stimulants used to manage attention-deficit/hyperactivity disorder, have been associated with decelerated linear growth in some children.

It is important to obtain a family history and a social history. Determination of parental heights, which is best accomplished by measuring the parents, is critical. This is particularly important in the child with short stature. Specific mid-parental height curves allow the physician to determine if a child's height is appropriate given parental stature.

A nutritional assessment is an essential part of the history. It is important to assess whether the child restricts his, her, or their food intake or avoids certain foods. The physician or another member of the health care team, such as a dietitian, can perform this assessment. A history of feeding problems may suggest the need for an evaluation by an occupational therapist. The dietary history can be determined by using a 24-hour recall of the child's intake during the previous day or a prospective 3-day diary in which a parent records the kinds and quantities of foods the child eats. This nutritional information can be used to find ways to alter the child's diet to ensure adequate and balanced meals.

Physical Examination

The essential component of the physical examination is determination of growth parameters. Calculation of the body mass index (BMI = weight [kg]/height [m]^2) is useful in children older than 2 years, and weight-for-length is useful in those younger than 2 years. The child with a low BMI is experiencing an element of undernutrition, but the short child with a normal BMI is not. Infants and children younger than 2 years should be plotted on a weight-for-length curve to determine their degree of undernutrition or overnutrition. The World Health Organization has developed and distributed growth curves for children up to 24 months of age. These curves reflect optimal rather than average growth and were developed from a longitudinal study of healthy breastfed infants. These curves, as well as those for individuals older than 2 years, can be accessed at www.cdc.gov/growthcharts/who_charts.htm. Measuring arm circumference and triceps skinfold thickness is also useful and provides information about body composition that is not obtained by height and weight. Children should be evaluated for dysmorphic features (eg, limb length discrepancy in Silver-Russell syndrome). It is important to remember that children with Down syndrome grow at different rates than other children, and separate standardized curves for assessing these children are available (see Chapter 42). Separate curves are also available for children with Turner syndrome and Williams syndrome as well as other disorders. The presence of 1 major congenital anomaly or 2 minor anomalies is suggestive of the existence of other anomalies and the chance of a genetic syndrome. The incidence of growth hormone deficiency is reportedly higher in children with cleft lip and palate. Children with heart murmur may have FTT related to CHD or to a syndrome such as Williams syndrome, in which the heart disease is but 1 feature.

Infants with environmentally related FTT exhibit certain behavioral characteristics that are easily recognized. These infants avoid making eye contact and exhibit gaze avoidance. They are not cuddly and do not like being held. When held, they may arch their backs in an effort to avoid the holder. Their muscles seem tense, and they are often considered to be hypertonic. These children may also exhibit specific disabilities, including oromotor dyspraxia and sensorymotor disorder, and they may demonstrate food texture aversion or difficulty with chewing and swallowing (ie, sensory food aversion). Children with neurologic disabilities often exhibit difficulties with oral skills.

Psychosocial Assessment

The evaluation of children with FTT and their families entails a detailed psychosocial assessment to determine what environmental factors may be affecting children's growth. Such an assessment is helpful even if the FTT has a medical basis because chronic disease affects family functioning. An extensive psychosocial evaluation focusing on the social determinants of health (eg, living conditions, adequacy of food supply, economic resources) and adverse childhood experiences (the latter particularly of the caregivers) can be carried out by the primary care physician (see Chapters 141 and 142, respectively).

Laboratory Tests

Routine laboratory tests appropriate for any pediatric health maintenance visit should be obtained in the child with FTT if these studies have not been performed recently. Such tests include hemoglobin, lead level (screening as determined by risk factors and geographic area), and urinalysis. Other laboratory tests are indicated by the findings in the history and physical examination. For instance, stool for ova and parasites should be obtained in a child with diarrhea who has immigrated from or spent time visiting a developing country. No recommended uniform diagnostic evaluation for FTT exists. Evaluation for endocrinopathies, such as hypothyroidism or growth hormone deficiency, should be carried out in the child whose bone age is less than the height age or who exhibits symptoms of these disorders. Genetic consultation or chromosomal assessment should be performed in the child with dysmorphic features or in families with a history of fetal wastage.

Imaging Studies

Radiography to determine bone age is useful in the child with short stature that is not related to parental heights. As stated previously, the child with familial short stature has a bone age the same as the child's height age and chronologic age. The child with constitutional delay has a bone age that is consistent with the child's height age but below the chronologic age.

Management

Any recognized underlying medical problem (eg, nephrogenic diabetes insipidus) should be managed appropriately. The child with IUGR who is not demonstrating catch-up growth may be a candidate for growth hormone therapy. Consultation with pediatric endocrinology is warranted.

Adequate Caloric Intake

Ensuring that a child receives appropriate caloric intake is essential. The caloric intake, which averages 120 to 150 cal/kg per day for most infants, should be based on the ideal weight rather than actual weight (see Chapter 28). For the infant on formula, the physician should review the exact preparation of formula with the mother. Overly diluted formula results in an unusually large intake volume with a lack of weight gain. For the infant who is breastfed, the physician should observe a feeding session to be certain the mother has an adequate milk supply and the infant is able to suck and swallow appropriately (see Chapter 29). The breastfed infant can be weighed before and after feeding to estimate the volume intake if concern exists about the adequacy of the mother's milk supply. Some infants with FTT have neurologic problems that prevent them from sucking and swallowing consistently without becoming fatigued.

The infant who is a slow feeder may require formula concentration (Table 146.1). These infants may also receive added calories in the form of glucose polymer (eg, Polycose) or oil, such as medium-chain triglycerides, mixed in the milk. The older child may be placed on supplemental feedings, such as PediaSure, Boost, or instant breakfast drinks, prepared with whole milk. Instant breakfast drinks are a less expensive form of nutritional supplementation than proprietary nutritional formulas, are well tolerated, and are available in different flavors (ie, vanilla, chocolate, strawberry). Up to 24 ounces per day of the breakfast drinks can be consumed and are given in addition to, not in place of, a balanced diet.

Table 146.1. Concentration of Infant Formula to Increase Caloric Intake

Concentrated Infant Formula (13-oz can)		
Formula (oz)	*Water (oz)*	*Calories (cal/oz)*
13	13	20
13	10	23
13	8	25
Powdered Formula		
Formula (scoops)	*Water (oz)*	*Calories (cal/oz)*
1	2	20
5	8	25

One food supplement that has been used globally to treat severe acute malnutrition is ready-to-use therapeutic food (eg, Plumpy'Nut, a peanut-based paste with sugar, vegetable fat, and skim milk and enriched with vitamins and minerals). It is not used in the United States and has variable acceptance in developing nations, in which up to 60% of caregivers report problems with acceptability of taste.

The mother should be advised that many children preferentially tolerate 6 small meals a day rather than 3 large ones. Additionally, the parent or guardian should be advised that access to non-nutritional foods, such as cookies, adversely affects children's appetites. Excess consumption of fruit juices should also be limited because it decreases the intake of other foods and may induce diarrhea. The physician should inform the parent or guardian about foods that can be added to the child's diet to increase caloric intake, including powdered milk, cheese, sour cream, avocado, and peanut butter. Often, children have a few favorite foods. Although food variety is appealing to adults, many children prefer a small number of nutritious foods. They should be allowed to consume these foods freely.

Children with neurologic disorders and associated problems with chewing and swallowing may require chronic *gavage*, that is, feeding through a gastric feeding tube.

Parenting Issues

Some parents need more help with appropriate child-rearing practices than the physician can provide. These parents can be referred to parenting programs that address multiple aspects of the parenting process. The mother with a substance use problem may need to participate in drug treatment programs (see Chapter 148). Other caregivers may need individual counseling for depression or emotional problems (see Chapter 24).

In some middle-class families, mealtime has evolved into a battle of wills. For some children eating at school is more enjoyable than than eating at home and they benefit from the social atmosphere of dining with their friends. The parent or guardian should be counseled about avoiding conflicts about meals with children, because the children win simply by closing their mouths. The caregiver should be encouraged to allow toddlers independence around mealtime. Eating in front of the television, however, should be discouraged.

Families may also require supplementary services to ensure that food supplies are adequate and financial resources sufficient. Such services include the Supplemental Nutrition Assistance Program (SNAP; formerly food stamps); the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); and Temporary Assistance for Needy Families (TANF).

Regardless of the individual needs of the family, it is critical that the physician craft a therapeutic alliance with the child's caregivers.

Home Visitation

Home visitation services provide useful diagnostic information and help the parent or guardian implement advice. Such information may include lack of access to running water, overcrowding, and inadequate food resources. Home visitation may be available in the community through the use of public health nurses or private visiting nurse agencies. These nurses should interact with the primary care physician to enable determination of families' compliance with treatment recommendations.

Child Protective Services

Involvement by child protective services may be necessary if the parent or guardian is unable to comply with medical recommendations, the child does not grow, or intentional neglect on the part of families is occurring. In some families with children with FTT, the home environment is not safe for children, and children require placement elsewhere. Families in which 1 child is singled out as "bad" and is intentionally neglected need immediate referral to child protective services, and some families overwhelmed by multiple problems, including parental substance use, also need such a referral to additional community resources.

Hospitalization

Hospitalization is occasionally necessary if the infant with FTT is severely malnourished, and food must be given in a controlled environment to assess the infant's ability to gain weight. Additionally, the infant with intercurrent illness may require inpatient care. Alternatively, a health professional may determine that the home environment is unsafe and that no other placement (eg, foster care) is available and that hospitalization is therefore indicated.

If concern exists for refeeding syndrome, the patient should be admitted to the inpatient setting. This syndrome was first described during World War II in Japan, and data on the condition in children are limited. The disorder encompasses a severe electrolyte imbalance in which the serum level of intracellular ions (eg, phosphate, magnesium, potassium) is low, and *refeeding syndrome* occurs when a patient moves from a catabolic to an anabolic state. Refeeding syndrome is best managed by a multidisciplinary team focusing on early correction of phosphates, magnesium, and potassium, correcting any acid-base imbalance, vitamin (thiamine) supplementation, and slow low-energy refeeding.

Regardless of etiology, the child with FTT usually gains weight in the hospital. Thus, hospitalization of the child with FTT simply to demonstrate appropriate weight gain in a different environment is considered neither appropriate nor cost-effective. Some insurance companies do not pay hospitals for inpatient management of children with FTT. Additionally, some children with environmentally related FTT do not gain weight in the hospital because they are subjected to many diagnostic tests that interfere with nutritional intake (eg, receiving nothing orally while awaiting the procedure), and they acquire nosocomial infections.

Prognosis

Many children with FTT respond dramatically to change in diet or environment. Improvement in affect and cognitive functioning frequently follows nutritional improvement. These children grow and both achieve and maintain normal stature. With early intervention, cognitive abilities also can be fully realized. Even when intervention has been delayed, catch-up growth and development are expected, although 25% to 30% of affected children may have weight and occasionally height below the fifth percentile. Continued monitoring for residual psychosocial or neurodevelopmental disabilities is appropriate even after growth has normalized. School performance and cognitive outcome in children who have experienced FTT are poorer than in children who have not experienced FTT. It is unclear if this association is related to early iron deficiency anemia, lack of calories or other micronutrient deficiencies, or psychosocial-environmental deficits.

CASE RESOLUTION

The term child had a low birth weight, which suggests IUGR. Although the mother reports using no alcohol or drugs, such denial is not uncommon. The child's growth pattern should be determined to learn if the rate of growth has changed recently, and BMI should be calculated to check for undernutrition and short stature. A mid-parental height curve should be used to determine if the child's short stature is related to the parents' short stature. Intervention should involve mobilizing resources for the child and family to ensure adequate food as well as financial and emotional support.

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CHAPTER 147

Fetal Alcohol Syndrome

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CASE STUDY

A 6-year-old boy is brought into the clinic by his maternal aunt, who expresses concerns about her nephew's behavior that are echoed by his kindergarten teacher. The teacher has reported that the child has a limited attention span and is often disruptive in class. The child's growth parameters have remained at the third percentile since birth. He has a smooth philtrum, thin upper lip, and short palpebral fissures.

Questions

1. What conditions and birth defects are included under fetal alcohol spectrum disorder?
2. What are the diagnostic criteria for fetal alcohol syndrome?
3. What is the differential diagnosis of the facial characteristics of fetal alcohol syndrome?
4. What typical behavioral and learning problems are experienced by the child with fetal alcohol syndrome?
5. What therapeutic interventions are appropriate to recommend for the child with fetal alcohol syndrome?

Fetal alcohol spectrum disorder (FASD) encompasses the spectrum of clinical findings caused by prenatal alcohol exposure. The 4 subcategories of FASD are fetal alcohol syndrome (FAS), partial FAS, alcohol-related neurodevelopmental disorder, and alcohol-related birth defects. A diagnosis of *partial FAS* requires facial dysmorphism in addition to growth disturbances or central nervous system (CNS) abnormalities. *Alcohol-related neurodevelopmental disorder* involves the functional impairments associated with prenatal alcohol exposure; however, clear diagnostic criteria are still being developed. *Alcohol-related birth defects* include structural birth defects that are associated with, but are not specific for, prenatal alcohol exposure (Box 147.1). This chapter will focus on FAS.

Fetal alcohol syndrome is a clinical diagnosis necessitating careful evaluation by an experienced physician to recognize the physical, behavioral, and cognitive abnormalities in an affected child. Diagnosis may be made at birth, but often the condition is not diagnosed until school age. Fetal alcohol syndrome has been recognized in the medical literature for decades and in historical literature for centuries; however, refining the criteria for diagnosis has been an ongoing process. Several entities have created guidelines to help analyze children with FAS, but in 2004, the Centers for Disease Control and Prevention (CDC) published broad-based criteria that are helpful for several reasons (Box 147.2). First, they educate physicians and caregivers about the wide spectrum of phenotypes that manifest after prenatal alcohol exposure. Second, they use the most recent CDC criteria for FAS, which helps capture the greatest number of potentially affected children with the goal of providing earlier intervention with a wider scope of services. Criteria must be met in all 3 categories of facial features, growth problems, and CNS abnormalities. For the patient with suspected FAS but for whom diagnostic criteria are incompletely met, the term FASD may be used to couch the findings, especially in the setting of confirmed maternal alcohol exposure. In the future, diagnostic criteria may be developed for other subcategories of FASD. Currently, however, the term FASD is not intended for diagnostic purposes but rather a descriptor of recognized phenotypes along a spectrum leading up to FAS.

Part of the difficulty in delineating a phenotype for alcohol exposure is that the degree of exposure is variable during embryogenesis (and organogenesis); factors include quantity ingested, concomitant drug exposures, malnutrition, and individual genetic responses to exposure. This wide variability in degree of exposure and individual response results in a multitude of clinical presentations.

Epidemiology

Prenatal alcohol exposure is much more common than the number of diagnosed cases of FAS would suggest. It has been estimated in surveys of women of childbearing age in the United States during 2011-2013 that approximately one-half of nonpregnant women of childbearing age reported some alcohol consumption and approximately 18% reported binge drinking (>4 drinks on 1 occasion) in the past 30 days. Among pregnant women, approximately 1 in 10 reported any alcohol use and 3% reported binge drinking in the past 30 days. Although estimates of children affected by FAS vary by region and population, an estimated 1 in 1,000 live births would meet criteria for diagnosis.

The estimate jumps 10-fold when certain high-risk groups are the focus. Approximately 1 in 100 children in foster care and nearly that many Native American children (3–9 per 1,000) meet criteria for diagnosis of FAS. Inclusion of children who meet some but not

Box 147.1. Physical Findings and Malformations Associated With Prenatal Alcohol Exposure

Cardiac
- Atrial or ventricular septal defects, aberrant great vessels, and tetralogy of Fallot

Skeletal/Extremity
- Shortened fifth digits, clinodactyly (ie, curved fifth digit), radioulnar synostosis, Klippel-Feil syndrome, flexion contractures, hemivertebrae, camptodactyly (ie, flexion contracture of digit), scoliosis, short metacarpals, short/webbed neck, hockey stick palmar crease

Renal
- Aplastic, dysplastic, hypoplastic kidneys
- Ureteral duplications, hydronephrosis, horseshoe kidney

Ocular
- Strabismus, refractive problems secondary to small globes, ptosis
- Retinal vascular anomalies

Auditory
- Conductive hearing loss, neurosensory hearing loss

Skin
- Hemangiomas, hypoplastic nails

Genitourinary
- Hypoplastic labia majora

Facial Features That Are Common but Not Required for Diagnosis
- Railroad track ears
- Epicanthal folds
- Flat nasal bridge
- Cleft lip

Box 147.2. Diagnostic Criteria for Fetal Alcohol Syndrome: Centers for Disease Control and Prevention[a]

- Facial features (all 3 required, with findings based on racial norms)
  - — Palpebral fissure length ≤10th percentile for age
  - — Smooth philtrum (University of Washington Lip-Philtrum Guide rank 4 or 5)
  - — Thin upper lip (University of Washington Lip-Philtrum Guide rank 4 or 5)
- Growth parameters (≥1 required at any age [not height for weight])
  - — Height ≤10th percentile
  - — Weight ≤10th percentile
- Central nervous system abnormalities (≥1 of the following):
  - — Structural (1 required)
    - Head circumference ≤10th percentile for age and sex
    - Brain abnormality at imaging
  - — Neurologic
    - Seizures
    - Measured delay in motor skills
    - Abnormal neurologic examination not attributed to another condition
  - — Functional (1 required)
    - Cognitive delay or global developmental delay (<3rd percentile)
    - Deficits in ≥3 functional domains (<16th percentile)
      1. Cognitive
      2. Executive function
      3. Motor function (fine or gross)
      4. Attention-deficit/hyperactivity disorder symptoms
      5. Deficits in social skills
      6. Other (eg, sensory, memory, language)

[a] Criteria must be met in all 3 overall categories (facial features, growth problems, central nervous system abnormalities) for a diagnosis of fetal alcohol syndrome.
Adapted from *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis.* Atlanta, GA: Centers for Disease Control and Prevention; 2004. https://www.cdc.gov/ncbddd/fasd/documents/FAS_guidelines_accessible.pdf.

all criteria for FAS results in a prevalence of 1% to 5% or higher in high-risk populations.

Pathophysiology

Alcohol is a teratogen, and like other teratogens its effect on the developing fetus depends on several factors, many of which are difficult to record. Although it is important to ask about the timing, quantity, and pattern of prenatal alcohol exposure, it is often difficult to obtain an accurate history. Additionally, because of genetic differences in women's ability to metabolize ethanol by alcohol dehydrogenase, each fetus receives a unique "dose" during gestation. Also individualized is each woman's nutritional intake and use of other drugs or medications. Alcohol acts as a toxin to cause damage and apoptosis to neurons in the fetal brain. Alcohol also inhibits proper migration, development, and functioning of cells during embryogenesis, contributing to structural anomalies in multiple organ systems, such as the kidney, heart, and brain.

Clinical Presentation

Signs and symptoms of FAS may be recognized at birth or not until later in childhood. At birth, a neonate may present with asymmetric intrauterine growth restriction, small for gestational age, head circumference disproportionately smaller than the body, or appropriate for gestational age. A variety of birth defects have been associated with fetal alcohol exposure, and many of these have been demonstrated in animal models. A newborn may exhibit signs of withdrawal from alcohol or concomitant drug exposure. With time, the infant may demonstrate failure to thrive or poor weight gain resulting from poor nursing. Infants exposed to alcohol in utero also present with nonspecific symptoms of irritability and dysregulated sleep patterns. In toddlerhood, developmental delays may be recognized by a caregiver or during developmental screening questions by a primary care physician. As a child approaches school age, a teacher may report behavioral concerns and poor school performance. Concerns such as distractibility, hyperactivity, and difficulty processing multistep directions may be raised in school. Additionally, a child may exhibit signs of fine motor delay, such as difficulty tying shoes or fastening buttons. Deficits in visual-spatial and math concepts are common for children with fetal alcohol exposure. Age-appropriate social skills are lacking in affected children, who often do not develop

street smarts. They take the blame, succumb to peer pressure, and are oblivious to social norms. Approaching the teenage years, the classic facies may become less distinctive. As teenagers mature, their cognitive and behavioral weaknesses predispose them to mental health issues, such as depression, anxiety, and problems with substance abuse.

Diagnosis

Facial Dysmorphia

Three classic facial features are required for the diagnosis of FAS. The characteristics are typical of midface hypoplasia and include short palpebral fissures, smooth philtrum, and thin upper lip. Other facial characteristics, such as epicanthal folds and flat nasal bridge, may be present but are not required for diagnosis. To accurately measure the palpebral fissures, the child should look directly up while the distance between the endocanthion (inner corner of the eyelids) and the exocanthion (outer corner of the eyelids) is measured. Palpebral fissure length (PFL) must be less than 2 standard deviations below the mean for a diagnosis of FAS.

The University of Washington Lip-Philtrum Guides for white patients (and others with similar lips) and black patients (and others with similar lips), which account for ethnic differences in contour of lips, are used (Figure 147.1). The images are ranked 1 through 5, with 5 representing the most affected phenotype, with the thinnest lip and smoothest philtrum. For children of other ethnicities, a best approximate is used. To properly use the Lip-Philtrum Guides, the child's face should be relaxed to avoid the lip and philtrum appearing thinner and smoother. The physician should evaluate the child's face within a specific horizontal planar view to avoid the illusion of a thinner lip. Guidelines on how to use the images are available on the University of Washington FAS website (http://depts.washington.edu/fasdpn).

Growth Problems

The criteria for growth deficiencies may involve the child's weight or length or both at any time. With the CDC criteria, a patient may qualify to meet criteria for growth problems based on birth or postnatal measurements. The child's weight or length must be less than or equal to the 10th percentile for age and sex. It is important, however, to evaluate other organic and environmental etiologies of short stature or poor weight gain, such as poor nutrition. Considerations for small head circumference are accounted for in the CNS abnormalities.

Central Nervous System Abnormalities

The criteria for neurologic problems may be met several ways because children develop an array of cognitive, behavioral, and developmental deficits. Criteria for structural abnormalities are met by a head circumference at the 10th percentile or below at any age or 3% or less when the child's weight and height are less than 10%. An experienced neuroradiologist may detect an abnormally small cranial structure, such as the cerebellum or corpus callosum, on magnetic resonance imaging. Manifestations of structural abnormalities include seizure activity not attributed to another cause or other focal deficits. Other functional CNS abnormalities may not be recognized until the child enters school and is compared with peers.

Differential Diagnosis

The hazards of using a "gestalt approach" to diagnosing FAS can result in inappropriate stigmatizing labels and missed opportunity to diagnose another genetic disorder that may carry a different prognosis. Several syndromes share facial features of FAS (Table 147.1). Fetal alcohol syndrome should be considered a diagnosis of exclusion in cases in which in utero alcohol exposure cannot be confirmed.

Evaluation

It is important that an appropriately trained professional assesses the child for each component of diagnosis; however, initial data should be gathered prior to referral.

History

A confirmed history of maternal alcohol consumption is not required for diagnosis, according to the CDC guidelines, but it should be documented if available. The physician should ask the parent or parents in a nonjudgmental way about all risks to a child's development, including maternal alcohol use before and during pregnancy. Some less stigmatizing ways to ask about alcohol consumption include: When did you learn that you were pregnant? How much did you drink before you were pregnant and before you knew you were pregnant? How much does your partner drink? Regular screening of parental alcohol use should be incorporated into routine child health supervision and developmental surveillance.

A detailed developmental history is important to document, including feedback from teachers and child care providers.

Physical Examination

As detailed previously, the physician should document the child's PFL measurement and score on the Lip-Philtrum Guide. Current and previous height, weight, and head circumferences should be plotted on an appropriate growth chart. Any additional physical features may be recorded as well to support diagnosis.

Diagnostic Studies

No laboratory test can confirm the diagnosis of FAS or another diagnosis on the FASD spectrum. The lack of a forthcoming history of alcohol consumption by the mother is an additional obstacle to diagnosis. Some alcohol biomarkers may be obtained from the mother or the newborn when suspicion of prenatal alcohol exposure arises. Ethyl glucuronide, fatty acid ethyl esters, and phosphatidylethanol are some alcohol markers under investigation that may be obtained from hair, nails, blood, urine, umbilical cord blood, or meconium with varied sensitivities, specificities, and windows of detection. Consent for testing may be required.

Imaging studies to screen for cranial malformations are not currently recommended unless the child is experiencing focal neurologic deficits or seizure activity. Similarly, targeted imaging of other organ systems is warranted in the patient with signs of an abnormality (eg, echocardiography in the patient with heart murmur).

Consultation with a geneticist may be appropriate to rule out other disorders with similar phenotype (Box 147.1).

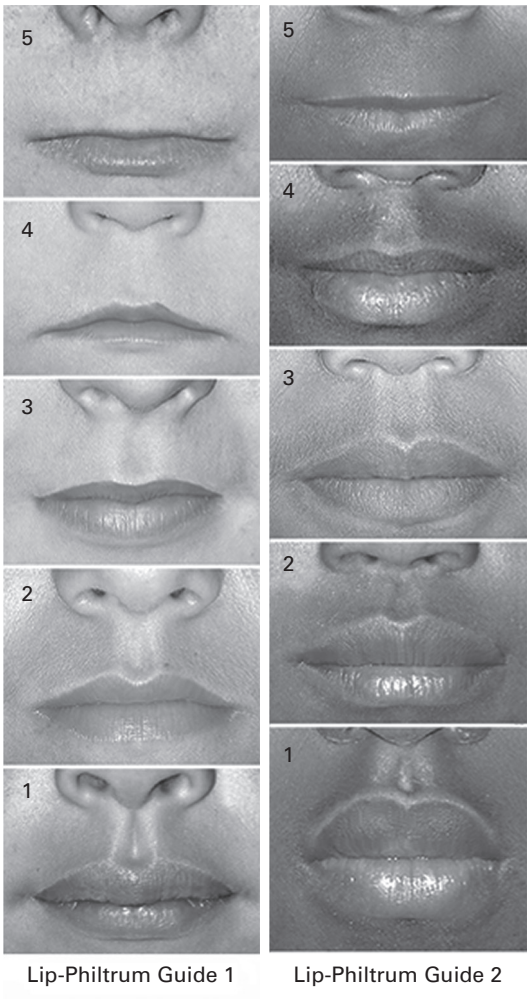

Figure 147.1. Lip philtrum guidelines for white patients and others with similar lips (left) and for black patients and others with similar lips (right). © and adapted with permission from Susan (Astley) Hemingway, PhD, University of Washington.

Management

Once a diagnosis related to alcohol exposure is suspected by a physician, the referral process should begin. A specialist in dysmorphology or an experienced physician may take the detailed measurements of the PFL and rank the facial features. Depending on local resources, evaluation of the patient by a multidisciplinary team is ideal. A child psychologist or developmental specialist can assess age-appropriate skills and need for therapeutic intervention. Only validated instruments should be used to test developmental capabilities. When delays are detected, referral to appropriate therapies should be initiated through early intervention services. An Individualized Education Program may be requested of the school by a caregiver who retains the child's educational rights. Public schools may provide occupational, physical, and speech therapies and social skills training. A psychiatrist may select therapies and medications particular to a child's unique mental health needs (see Chapters 133 and 134). Social workers are integral to providing support and additional resources to the family. As teenagers approach adulthood, referrals to vocational training and programs to transition young adults to independent living are important.

Table 147.1. Syndromes With Facies Resembling Fetal Alcohol Syndrome[a]

Syndrome	*Long or Smooth Philtrum*	*Thin Upper Lip*	*Small Palpebral Fissures*
Cornelia de Lange	+	+	–
Aarskog	+	–	–
Williams	+	–	+
Dubowitz	–	–	+
Toluene embryopathy	+	+	+
Brachmann-de Lange	+	–	–
Fetal valproate	+	+	–
Maternal phenylketonuria	+	+	+
Floating-Harbor	+	–	–
22q11.2 deletion (eg, DiGeorge, velocardiofacial, Opitz)	+	–	+

[a] Two additional syndromes with facies resembling fetal alcohol syndrome are fetal hydantoin syndrome (midface hypoplasia, wide-spaced eyes) and Noonan syndrome (low nasal bridge, wide-spaced eyes, epicanthal folds).
Abbreviations: +, present; –, absent.

Prognosis

Many of the neurotoxic effects of alcohol on the developing fetus have lasting sequelae. Early interventions may improve but not correct cognitive deficits and associated mental health issues of aging children and adults with FAS. The mental health disorders are thought to be the result of adverse childhood experiences (eg, ridicule, harassment, failures) related to a child's behavioral and cognitive deficits. Some of the mental health disorders include oppositional defiant disorder, conduct disorder, depression, adjustment disorder, anxiety disorders, substance abuse, and sleep disorders. Many adults with FAS do not finish high school and become unemployed or incarcerated. A fraction of adults with FAS require assisted living arrangements.

CASE RESOLUTION

The child meets diagnostic criteria for FAS. It is recommended to the caregiver that she initiate obtaining "educational rights" over her nephew so she can request an Individualized Education Program from his school administrator. An assessment for attention-deficit/hyperactivity disorder, such as the *Conners 3* or the *National Initiative for Children's Health Quality (NICHQ) Vanderbilt Assessment Scale,* or another standardized measure for this disorder, should be given to the caregiver and teacher to each evaluate the child. Prescription for stimulant medications may be warranted in conjunction with behavioral therapy. Depending on local resources, the caregiver and child may be referred for psychotherapy, including parent-child interactive therapy, in which the patient's aunt may be coached on how to cope with his behaviors in the most positive, effective manner.

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CHAPTER 148

Infants of Substance-Using Mothers

Sara T. Stewart, MD, MPH, FAAP

CASE STUDY

A neonate is born by emergency cesarean section because of abruptio placentae. The mother is a 29-year-old gravida 6, para 4, aborta 2 with a history of crack cocaine and heroin use during pregnancy. The newborn is 36 weeks' gestational age with a birth weight of 2,400 g (5.3 lb) and length of 43 cm (16.9 in). Physical examination is normal. The newborn does well for the first 10 hours but then develops jitteriness with irritability, diarrhea, sweating, and poor feeding. A urine toxicology test on the newborn and mother are positive for cocaine.

Questions

1. What complications affect the neonate secondary to in utero drug exposure?
2. What withdrawal symptoms does the newborn experience as a result of in utero drug exposure?
3. What typical behavioral and learning problems are found in the child with in utero drug exposure?
4. What are the appropriate treatment strategies for the neonate who has experienced in utero drug exposure?
5. How does the legalization of marijuana affect the counseling of the mother about breastfeeding?

Maternal substance use during pregnancy places neonates at risk for several medical, psychosocial, and developmental problems. The particular problems experienced by newborns depend on the drug (or drugs) to which they have been exposed; many have been exposed to multiple drugs in addition to cigarettes and alcohol. The long-lasting effects of alcohol exposure are well established (see Chapter 147), but the effects of newer drugs are less well defined. Illicit drugs change in their popularity, form of use, and availability at different points in time.

The environment into which a child is born also affects the child's health and development. Environments in which substance use is common are frequently suboptimal for normal growth and development because of the effect of substance use on parenting; fragmentation of families; intimate partner violence; incarceration of significant family members; illnesses, including HIV infection; limited financial resources; homelessness or substandard housing; unemployment; child abuse and neglect; and limited access to health care. Because of these environmental issues, many drug-exposed neonates are cared for by foster parents or nonparental family members. These factors also make it difficult to determine, in a given newborn, which problems are caused by the drug exposure versus accompanying environmental conditions. This differentiation is of less significance to the physician than the researcher or epidemiologist because the physician will care for the problems exhibited by the drug-exposed newborn regardless of etiology.

Epidemiology

In 2016, 13% of women between the ages of 15 and 44 years in the United States reported having used illicit substances in the past month, which is an increase from prior years. Although data collected via maternal self-report are typically an underestimate of prevalence, a national survey reported that 6.3% of women used illicit substances in the past month while pregnant. The same survey also found that 8% of women reported drinking alcohol and 10% reported smoking cigarettes in the past month while pregnant. Meconium analysis has demonstrated not only extensive differences in the prevalence of in utero drug exposure between hospitals (eg, public versus private) but has also shown differences in the substances of choice in different geographic areas. Polysubstance use is the most common clinical scenario in all communities, and national data on women of childbearing age have shown marijuana to be the most commonly used substance, followed by opiates, hallucinogens, cocaine, and methamphetamine.

Clinical Presentation

Many of the different substances that women use while pregnant can result in similar sequelae in the newborn, infant, or child. In utero growth restriction, irritability, disordered eating or sleeping, and hypertonicity may be seen in affected newborns and infants. Older children may have developmental delays, symptoms of attention-deficit/hyperactivity disorder, learning disabilities, or behavioral

difficulties (eg, oppositional or impulsive behavior). Prenatal exposure to opiates, such as heroin or methadone, may cause symptoms in the newborn of neonatal abstinence syndrome (NAS) (ie, drug withdrawal), including respiratory, gastrointestinal (GI), or nervous system effects, such as apnea, tachypnea, emesis, diarrhea, irritability, hypertonicity, tremors, seizures, temperature instability, and sneezing. Symptoms often occur within 72 hours of birth, but because of the long half-life of methadone, symptoms of methadone withdrawal may take up to 5 days to manifest.

Alcohol and cocaine have been associated with birth defects as well. Abnormalities such as absent limbs, cardiac defects, genitourinary anomalies, ocular anomalies, and microcephaly have been reported with cocaine exposure. Alcohol has been associated with a spectrum of effects, termed fetal alcohol spectrum disorder (see Chapter 147). Within this spectrum, a subset of patients fit the well-defined criteria for a diagnosis of fetal alcohol syndrome, including facial dysmorphology, growth deficiency, and neurodevelopmental disabilities. The presence of the following 3 sentinel features in the facial dysmorphology is the most sensitive and specific diagnostic finding for fetal alcohol syndrome: a flat philtrum, thin upper lip, and short palpebral fissures. The spectrum of neurodevelopmental problems includes diagnoses such as microcephaly and seizures, as well as many types of developmental, cognitive, and behavioral difficulties. Also included within fetal alcohol spectrum disorder is a category for alcohol-related birth defects, which includes anomalies such as congenital heart defects, skeletal deformities, renal anomalies, hearing loss, ophthalmologic abnormalities, and cleft lip and palate.

With the legalization of marijuana in some states, prenatal marijuana exposure is under increased discussion. Studies on marijuana exposure have shown inconsistent results on the neonatal outcomes of intrauterine growth restriction, increased arousal, and sleep disturbance. More consistent results exist concerning neurobehavioral effects on the older child. When tested in the elementary years, children exposed to marijuana in utero had an increased likelihood of difficulty with visual perception as well as memory and language tasks. Risk for attention difficulties is increased in childhood, and adolescents are at risk for problems with executive functioning.

Pathophysiology

Drugs used by pregnant women may affect newborns in 3 different ways: the drugs may be addictive and result in symptoms of withdrawal during the neonatal period; they may be toxic and lead to impaired functioning and neurodevelopmental disabilities; and they may be teratogenic and cause congenital anomalies and a dysmorphic appearance. The ultimate effects of the drugs are a complex interaction of environmental and genetic influences that are variable depending on the timing of the prenatal exposure. Differences in maternal metabolism of drugs result in differences in fetal exposure to toxins, and genetically determined differences in fetal susceptibility to the toxins lead to a spectrum of effects in exposed neonates. During gestation, the effects of drug exposure also vary depending on the timing of exposure. Each organ has a unique period of susceptibility as it forms during the first trimester. Prenatal substance exposure during this period is more likely to result in organ malformation. The second and third trimesters primarily involve organ growth, cell differentiation, and functional maturation of organs; thus, exposure during this period is more likely to result in growth abnormalities or functional difficulties. The specific effects of the different substances on the developing fetus can be understood in terms of their biochemical properties.

In utero exposure to opiates, such as heroin and methadone, results in physiological addiction. These drugs bind to opiate receptor sites in the brain and GI tract. When the drugs are no longer present after birth, the newborn experiences withdrawal. Animal models have also found that prenatal exposure to opiates can result in decreased density of cortical neurons and decreased development of neurons.

Cocaine and its metabolites cross the placenta and concentrate in amniotic fluid. Cocaine is toxic and teratogenic, and it interferes with 3 neurotransmitter pathways in the brain. Cocaine blocks the reuptake of norepinephrine. This is associated with tachycardia, hypertension, diaphoresis, and an increased incidence of preterm labor. Diffuse vasoconstriction may affect the placenta and result in anomalies such as placental infarcts or abruptio placentae. The fetus may also be affected by the vasoconstriction and its resultant hypoperfusion and ischemia and may develop anomalies, such as atresia of the GI tract, stroke, or absent limbs. Cocaine decreases the reuptake of dopamine. This effect is apparent in cocaine-using mothers who have decreased appetite and subsequent poor nutrition during pregnancy. Stereotypical behavior, hyperactivity, euphoria, confidence, and heightened sexuality may be associated with sexual promiscuity and increased risk of acquiring HIV and sexually transmitted infections (STIs). Cocaine decreases serotonin reuptake, resulting in decreased sleep. The sleep cycle of neonates who were exposed to cocaine in utero is often disrupted.

Methamphetamine is commonly manufactured from ephedrine or pseudoephedrine and has greater central nervous system (CNS) penetration than its metabolite, amphetamine. It has direct toxic effects on the CNS and causes increased release and decreased reuptake of dopamine, norepinephrine, and serotonin. These neurotransmitter alterations result in symptoms that are similar to those described for cocaine. A large prospective study of infants prenatally exposed to methamphetamine did not find increased risk of cardiac, skeletal, craniofacial, or respiratory issues, as had been previously reported; however, these newborns are at risk of being born small for gestational age.

Direct effects of methamphetamine use are dose- and frequency-dependent in the adult user. It has been shown to have cardiovascular, pulmonary, renal, and hepatic toxicity. Higher dose and increased frequency have also been associated with psychosis and toxicity to subcortical structures. More recent data have noted subcortical white matter and gray matter changes in children with prenatal exposure to methamphetamine.

Prenatal marijuana exposure results in toxic effects to the developing brain, with resultant risk of neurodevelopmental effects.

Existing studies show no association between cannabis use during pregnancy and fetal anomalies, but exposed neonates may show some mild symptoms of increased arousal and sleep difficulties; no physiologic withdrawal from marijuana occurs as does with opiates. Endogenous cannabinoid receptors are present in the fetal brain, and it is believed that exposure to exogenous cannabinoids results in supraphysiologic stimulation of the receptors. This, in turn, affects synaptogenesis and developing neurotransmitter systems.

Reports have documented the occurrence of withdrawal symptoms within days after birth in neonates with prenatal alcohol exposure, but more common effects of prenatal alcohol exposure are direct cellular toxicity and teratogenesis. The specific mechanism by which alcohol and its metabolites damage fetal tissues is unknown, but it has been shown to affect CNS neuronal migration and synaptogenesis. For a given level of alcohol intake, the precise level of fetal exposure to metabolites is likely to vary among women, depending on maternal genetic makeup and the resulting variability in alcohol metabolism. Timing of the exposure during different periods of development can also result in different teratogenic effects on the fetus. Exposure during the first trimester may affect organogenesis or craniofacial development; exposure in the second and third trimesters can cause poor growth and neurotoxicity. Maternal alcohol use may also be associated with poor nutrition, resulting in poor delivery of nutrients to the fetus.

Phencyclidine (PCP) has sympathomimetic effects, including increases in blood pressure, heart rate, respiratory rate, deep tendon reflexes, and tone. Additionally, PCP has cholinergic effects, causing sweating, flushing, drooling, and pupillary constriction. Neonates exposed to PCP in utero do not exhibit these symptoms but display neurologic and developmental disorganization.

Differential Diagnosis

Major differential diagnoses relate to the symptomatology produced by the used substance or substances (Box 148.1). Neonates exposed to addictive substances, most commonly opiates such as methadone and heroin, may present with symptoms of withdrawal (Box 148.2). Irritability and jitteriness may be symptoms of drug withdrawal or direct drug neurotoxicity but may also be caused by hypoglycemia, hypocalcemia, hypomagnesemia, and sepsis. Seizures occur in 1% to 3% of neonates exposed to heroin in utero, and the differential diagnosis for neonatal seizures includes intracranial hemorrhage, hypoxic-ischemic encephalopathy, CNS infection, CNS malformation, and metabolic disorders. Gastrointestinal symptoms, such as vomiting or diarrhea, may be confused with reflux, formula intolerance, obstruction, or infectious gastroenteritis.

Dysmorphic appearance may also be the result of alcohol or drug exposure. Fetal alcohol syndrome is the most clearly defined dysmorphic syndrome related to maternal substance use during pregnancy. In making such a diagnosis, other genetic disorders that may have overlapping findings should be considered as well.

Failure to thrive (FTT) may be a presenting symptom in the newborn, infant, or child with a history of in utero drug or alcohol exposure. (See Chapter 146 for a discussion of the differential diagnosis of FTT.) It is important to consider maternal substance use in all patients who have been diagnosed with FTT, particularly if they were born small for gestational age.

Older children may present with a wide range of neurodevelopmental and behavioral problems. Common behavioral symptoms include impulsivity, inattention, hyperactivity, and antisocial behavior. Although many of these symptoms have been correlated with prenatal drug exposure, postnatal environmental factors, such as continued parental substance use, violence, inconsistent or poor parenting, and foster care placement, are also significant contributors. As a result, it may be difficult to clearly determine the precise etiology of developmental and behavioral problems in a child exposed to drugs or alcohol.

Maternal substance use should be considered in all neonates who present with STIs such as syphilis, hepatitis B, hepatitis C, and HIV.

Box 148.1. Diagnosis of Newborns of Substance-Using Mothers

- Symptoms of withdrawal (see Box 148.2)
- Congenital anomalies
- Developmental delay and behavioral disorders
- Growth retardation
- Sexually transmitted infections

Box 148.2. Symptoms of Neonatal Abstinence Syndrome

- Irritability
- Jitteriness
- Tremors
- Hypertonicity
- Seizures
- Mottling
- Temperature instability
- Vomiting
- Diarrhea
- Apnea
- Tachypnea
- Sweating
- Poor feeding
- Sleeping difficulties

Evaluation

History

The possibility of maternal substance use should be considered in the setting of certain maternal risk factors, including the absence of prenatal care, evidence of poor maternal nutrition, poor maternal weight gain, presence of STIs, symptoms of acute intoxication, abruptio placentae, precipitous delivery, and a history of domestic violence.

The newborn with symptoms of withdrawal should be evaluated for the possibility of maternal substance use. This assessment involves an appropriate history as well as a toxicologic evaluation.

Mothers disclose their drug history to varying extents, depending on the circumstances of the interview. Mothers who are concerned about the health and well-being of their newborns and do not fear legal repercussions are more likely to discuss their drug use. An appropriate drug history should be obtained in a nonjudgmental manner (Box 148.3). Studies have shown that the use of a structured questionnaire rather than a cursory interview increases the incidence of reported substance use by 3- to 5-fold.

Physical Examination

The newborn should be assessed for common complications related to maternal substance use. A full physical examination should be performed to check for the presence of any malformations. Growth measurements should be noted, and the physician should evaluate for evidence of growth impairment or microcephaly. The preterm neonate should be monitored for problems related to prematurity, such as intraventricular hemorrhage and necrotizing enterocolitis. Assessment for signs of NAS should be done in the days after birth (Box 148.2). Neurologic and developmental status should be assessed and monitored at each visit. Abnormalities such as hypertonicity, coarse tremors, and extensor leg posture are frequently noted in the neonatal period, and disturbances in fine and gross motor coordination may persist through the toddler years.

Laboratory Tests

In addition to obtaining a toxicologic history, screening for drugs should also be performed. The legal guidelines for screening mothers for drugs vary in different localities. Generally, if clinical symptoms indicate a need, a neonate can be screened on medical grounds without specific parental consent because the information obtained is important in the care of the newborn. Screening of the mother's urine without her consent is more problematic, however, because of the potential legal implications of a positive test result.

Drug testing of the infant can be performed on urine, meconium, hair, or the umbilical cord; urine and meconium testing are the most commonly used techniques, however, because they are noninvasive, inexpensive, and widely available. Urine testing can detect drug exposure within the 3 days before specimen collection, and meconium testing can detect exposure after 20 weeks of gestation. Meconium is more sensitive and specific than urine testing but is more sensitive to specimen collection and storage technique. The best results are often obtained from a combination of maternal urine and newborn meconium testing. It is important to realize that a negative screening test result does not rule out the possibility of exposure, because a drug metabolite may be present but not to the level of the detection threshold of the particular test. Newer techniques include neonatal hair and umbilical cord analysis. Hair analysis can detect drug exposure in the third trimester, and it remains unclear what time frame is reflected in umbilical cord testing.

Most screening tests of urine, meconium, and hair samples use immunoassay techniques, which are inexpensive and sensitive but not very specific. False-positive results may be obtained for multiple illicit substances. Common scenarios include a positive amphetamine screening result in a patient who has taken over-the-counter medication containing ephedrine or pseudoephedrine, or a positive opiate screening result in a patient who is using cough medicine with dextromethorphan. For this reason, and because of the potential legal implications of a positive result in this setting, it is strongly recommended that positive immunoassay results be confirmed with further testing of the sample via gas chromatography or mass spectrometry.

Further evaluation in the neonatal period should include an evaluation for the presence of STIs, particularly HIV, hepatitis B, hepatitis C, and syphilis.

Box 148.3. What to Ask

Newborns of Substance-Using Mothers

- During the pregnancy, did the mother use any substances, such as alcohol, cigarettes, marijuana, or prescription or illicit drugs?
- Has she ever used these substances? Is she currently using these substances?
- If so, how much? How frequently? By what route? To what extent is she trying to abstain?
- Is the mother at risk for sexually transmitted infections? Has she ever been tested?
- Did the mother have prenatal care? When did the care start?
- What is the status of other children in the family?
- Does the partner use any substances such as alcohol, cigarettes, marijuana, or illicit drugs?

Imaging Studies

No routine imaging has been recommended based solely on a history of substance exposure in utero. Instead, imaging should be directed by symptomatology. For example, the newborn with a heart murmur and history of prenatal alcohol exposure warrants a cardiac evaluation and possible echocardiography. Additionally, the newborn with prenatal drug exposure and abnormal neurologic examination should undergo a thorough neurologic evaluation, which may include neuroimaging.

Management

In the neonatal period, treatment of the newborn exposed to drugs in utero requires attention to associated conditions such as preterm birth, in utero growth restriction, and in utero infection with STIs.

The first approach to managing NAS involves nonpharmacologic methods. The goal of this approach is to create a calm, soothing environment that minimizes stimulation to the baby. Common symptoms of irritability, crying, and poor sleeping are managed with swaddling, cuddling, and gentle manual rocking. The swaddling helps minimize stimulation and promotes longer durations of sleep, and the gentle tactile sensation of cuddling and rocking is also beneficial. Other techniques for minimizing stimulation in infants include using dim lighting and low-noise environments. Feeding is often frequent and is done on demand to minimize irritability. When

possible, rooming-in of infant with mother is recommended to promote bonding and breastfeeding, both of which have been shown to reduce the incidence and severity of symptoms with NAS. Some exposed newborns may have slow or disordered feeding and may require evaluation by an occupational therapist, lactation consultant, or nutritionist as well. Breastfeeding is not restricted for mothers unless the mother is continuing to use illicit drugs, has polysubstance use, or has HIV infection.

The assessment of withdrawal symptoms in the neonate typically is done using a standardized scoring tool to assist in the documentation of symptom severity. After scores reach a threshold level, pharmacologic treatment may be required. Although no known ideal drug and dosing regimen exists for the management of NAS, the best method for reducing the duration of newborn hospital stay and the duration of NAS treatment is the establishment and use of standardized treatment protocols that are based on best practices. For the neonate exposed to an opiate in utero, treatment has traditionally been with an opiate, such as methadone or morphine. Morphine is often preferred over methadone because of its shorter half-life, which results in the ability to titrate doses more rapidly. More recently, sublingual buprenorphine has been studied and is being used in the management of NAS. Compared with the opiates, buprenorphine has been found to result in shorter durations of treatment and shorter hospital stays. Phenobarbital is used in cases of nonopiate exposure or as an adjunct to morphine or methadone. Diazepam, paregoric, and tincture of opium are no longer used because of toxic ingredients or associated complications. Medications should be tapered over time, allowing infants to outgrow the dosage.

Involvement of social services is also a key component of management. In many jurisdictions, child protective services must be notified of positive toxicologic test results on newborns or their mothers. Likewise, it may also be necessary to report to these agencies if a newborn displays symptoms of neonatal drug withdrawal. These agencies are generally responsible for performing a home assessment and determining the adequacy of the home environment. In some cases, the newborn may be assigned to a foster home and the parent or parents may be ordered to participate in a drug treatment program and parenting classes.

After the newborn period, the focus of management is on the provision of well-child care and developmental monitoring. Attention should be paid to physical growth and administration of immunizations. If a sensory impairment or neurodevelopmental delay is apparent, the child should be referred to appropriate community agencies for services. Federal programs that operate under the Individuals with Disabilities Education Act provide interventional services for disabled and at-risk children 6 years and younger.

Symptoms of attention-deficit/hyperactivity disorder or other behavioral problems in older children may require intervention, with recommendation for specific school programs as well as pharmacologic treatment. Regular assessments of school performance should be obtained from children's teachers. Standardized neurodevelopmental tests should be administered at periodic intervals to ensure appropriate progress.

Prognosis

Many neonates, particularly those exposed to alcohol in utero, experience long-term sequelae and disability. Most commonly, these effects are subtle but can have far-reaching effects for the child. Remedial educational programs help manage but do not cure problems. Recent studies have shown that for children who were exposed to drugs, the environment in which they are raised is a significant factor affecting their ultimate outcome. A stable, nurturing environment minimizes the many adverse effects of prenatal drug exposure and promotes normal neurodevelopment by enforcing the acquisition of skills and knowledge.

CASE RESOLUTION

The case study highlights typical features of the neonate who was exposed to drugs in utero. Management includes testing for hepatitis B, hepatitis C, syphilis, and HIV and administering medication, such as morphine, methadone, or phenobarbital, if irritability does not respond to swaddling or other measures. The situation should be reported to child protective services to ensure an assessment of the neonate's home environment.

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CHAPTER 149

Divorce

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CASE STUDY

A 7-year-old girl who has been your patient for 5 years is brought in by her mother for abdominal pain that occurs on a daily basis and is not associated with any other symptoms. The pain is periumbilical. In obtaining the history, you learn that the father has moved out of the home and the parents plan to divorce. The mother believes that her daughter's symptoms may relate to the impending divorce, and she wants to know what else to expect.

Questions

1. What are the problems faced by children whose parents are undergoing divorce?
2. What are the age-related reactions of children in families undergoing divorce?
3. What are the custodial issues and arrangements after divorce?
4. What is the role of the pediatrician in counseling families undergoing divorce?
5. What anticipatory guidance can be offered about custody and remarriage?
6. How can the pediatrician help stepfamilies adjust?

Divorce is a legal term meaning the legal conclusion or dissolution of a marriage. Divorce has been equated to the "death" of a marriage and in some ways may be more devastating for children than the death of a parent. When a parent dies, that parent becomes idealized in the mind of the child, but when parents divorce, the noncustodial parent is often devalued. Even with a joint custody arrangement, each parent is frequently criticized by the other. For the child, the parents are no longer the ideal figures they once were. The challenge for the pediatrician is to maintain a neutral position, be supportive, and serve as a source of advice and guidance. Remaining neutral may be challenging because much of the contact may have been with 1 parent—usually the mother.

The pediatrician plays a specific and potentially unique role in caring for children experiencing parental divorce because other resources may be few and other agencies or individuals may lack an antecedent relationship with the family. Extended families are often geographically distant and less available to provide help. Religious institutions have often failed to assume a counseling role in this area; some religions view divorce unfavorably. Most families do not routinely seek out mental health services unless problems are more apparent. Therefore, it is critical for the pediatrician to become involved in anticipatory guidance of families considering and undergoing divorce. It is important to recognize that divorce is not a single event; rather, it is a process that occurs over time, and parental separation may antedate the actual divorce by months or even years. Anticipatory guidance focuses on preparing children and families for times ahead. Additionally, the pediatrician serves as a child advocate. The parents themselves are often so consumed by their own emotional turmoil that they may not be available or are not even aware of the stress and trauma their children are experiencing. The pediatrician should be knowledgeable about the effect of divorce on children and their subsequent psychological development. Additionally, the pediatrician can help as new families form, assisting the transition of caregivers into the role of stepparents and children into becoming stepsiblings.

Epidemiology

Divorce affects nearly 50% of marriages, although the rate recently has decreased to closer to 40%, attributed in part to the decrease in the marriage rate. In fact, separation of unmarried heterosexual partners is far more common than divorce between married individuals. Approximately 40% of all births are to unmarried women. Socioeconomic differences exist, with 11% of higher income parents divorcing as opposed to 17% of lower income couples. Divorce is more common among those who have served in the military. Couples are less likely to divorce while they remain with the military, instead divorcing after they leave the service. Veterans are 3 times as likely to be divorced as those who have never served.

The median length for a marriage in the United States is 11 years. On average, there are 800,000 divorces a year, and 90% of divorces occur outside of court. A divorce may be collaborative (ie, uncontested), in which the parents negotiate an agreement with the advice of a separate attorney for each parent. *Mediated divorce* involves a mediator but no attorneys, to reach an agreement. Children do not routinely have legal representation in the process. Mediators may assist in establishing visitation schedules and in general, children do not participate in these meetings either.

The legal profession has been endorsing greater focus on and participation of children in divorce disputes. Approximately 1.5 million children per year are affected by divorce. Nearly one-third of all

children live in households in which parents are divorced or remarried. Children between age 3 and 8 years are the major age group affected. Children involved with parental divorce require at least 2½ to 3 years to regain their equilibrium and master a sense of control, although developmental challenges may continue to emerge at different times after the divorce.

Divorce usually results in reduced economic resources to mothers and children. In the first year after divorce, the mother's income is reduced to 58% of the predivorce level. Even after 5 years, income for mothers and children is only 94% of the predivorce amount; for intact couples, income has risen to 130% during that period. Decreased income is often associated with multiple moves to more affordable housing, along with change in schools and loss of friends. More affordable neighborhoods may not provide the same resources and environment to which the children were previously accustomed.

Types of custody include sole, joint, legal, and physical. The types of custody define the legal responsibilities of each parent as well as the time spent between parent and children. *Bird's nest custody* is a unique form of joint custody in which children remain in the home and the parents take turns moving in and out. This is less common than other arrangements. Many states now promote joint custody, which is associated with higher levels of involvement by the biological father, increased child support payments, and greater paternal satisfaction. Issues of remarriage and stepsiblings are also important. Eighty percent of divorced men and 75% of divorced women remarry, and 40% of these remarriages end in divorce. As a result of the high rate of remarriage, 1 in 3 children in the United States has a stepparent. Eighty-six percent of stepfamilies include the biological mother and a stepfather. Children in stepfamilies often must readjust to differing roles in differing households and differing relationships between their biological parents, stepparents, biological siblings, and stepsiblings.

Psychophysiology

The experience that children have following parental divorce is influenced by many factors. When a divorce is contentious and children are exposed to hostility between their parents, high levels of stress can result in physiologic changes, including elevated levels of cortisol, which can be associated with sleep disturbances, anxiety, irritability, and weight change.

The individual child's temperament and personality also affect the child's adjustment to parental divorce. An easygoing child with strong self-esteem and a positive outlook fares better than a less easily adaptive child with a less optimistic personality. The reaction to divorce also depends, to a large extent, on the age of the child (Table 149.1). Generally, children do not have the cognitive ability to understand the meaning of divorce until they reach 9 or 10 years of age. The experience is also different for children without siblings, that is, "onlies." Not only do they lack brothers or sisters with whom to commiserate, they may also experience parental overconcern, manifested by being asked repeatedly how they are feeling and how they are doing. Studies have demonstrated that the negative effect of parental divorce on adolescent academic performance is mitigated by increased sibship size.

Table 149.1. Children's Reaction to Divorce by Age

Age	*Symptoms*
2½–4 years	Regressive behavior
5–6 years	Whiny, immature behavior
6 years–preadolescent	Disequilibrium Depression Somatic symptoms Poor school performance
Adolescence	Anxiety Depression Risk-taking behavior Substance/alcohol use Delinquency

Infants and toddlers (up to age 2 years) react to changes in routine and may experience sleeping and feeding disturbances, as well as increased spitting up and clinginess. Between 2½ and 4 years of age, a child may exhibit increased separation anxiety and regressive behavior. The child becomes needy and dependent, with behavior characterized by irritability, whining, crying, fearfulness, and sleep problems. Aggression and regression, particularly in the area of toilet training, may manifest. One-third of children in this age group continue to exhibit regressive behavior 1 year after divorce.

Children between 3½ and 5 years of age often show more aggressive patterns of behavior with hitting, biting, and temper tantrums. Regressive behavior may also be seen. Young children feel particularly responsible for their parents' divorce (ie, the parents are divorcing the child). At this point in development, children experience what Piaget has referred to as an egocentric way of thinking. Self-blame, decreased self-esteem, and a high level of fantasy, particularly about parental reunion, are apparent. Approximately 1 year after divorce, 65% of these children still show decreased levels of functioning. Preschool-age children may repeatedly ask the same questions as a means of processing and assimilating the information. Such questioning should be met with patience and reassurance.

Children 5 to 6 years of age are often depressed and may exhibit behavior that is less mature or age appropriate. Girls in this age group seem to react more poorly than boys to divorce. Two-thirds of girls are less well-adjusted 1 year after the divorce, as opposed to only approximately one-fourth of boys. Children of this age may seem moody and daydream, whine, or have temper tantrums.

Children between 6 years of age and adolescence seem to experience profound disequilibrium, with feelings of shame, anger, and loneliness. This anger may manifest as antisocial behavior. Older children also talk about an overwhelming feeling of sadness and grief. Their somatic reports include headache, abdominal pain, and an increase in symptoms of preexisting medical conditions (eg, asthma). Sometimes the somatic symptoms of children, particularly those in the school-age group, are attributed by 1 parent to the poor living conditions at the other parent's household. It

is important for the physician to anticipate that 50% of children involved in parental divorce show a deterioration in their school performance. Therefore, the school should be notified about the pending divorce and changes in family structure. Decreased school performance is attributed to decreased ability to concentrate, sadness, and depression or decreased conduciveness to do homework in 1 household over the other.

Parental divorce is particularly difficult for adolescents, who describe it as "extraordinarily painful." Problems may emerge during adolescence, and adolescents may exhibit externalizing behavior (eg, delinquency, risk taking, alcohol use) and internalizing behavior (eg, anxiety, depression). The experience is worse for younger adolescents. During the first stages of divorce, they feel a personal sense of abandonment and a loss of parental love. Older adolescents are concerned about their future potential as marital partners. They also feel anxious about financial security, especially money for college. De-idealization of both parents is precipitous. Adolescent girls do better than boys early on, but this reverses with time. This pattern is referred to as a "sleeper effect" or "delayed effect," with girls subsequently feeling rejected and unattractive as they reinterpret their parents' divorce with their additional maturation. Divorce during adolescence sometimes results in precocious sexual activity or risk- or thrill-seeking behavior. Studies suggest that paternal involvement after the divorce reduces the risk of alcohol abuse. Adolescents from divorced families are more likely to experience teenage parenthood. Adolescent girls from divorced families are less likely to succeed academically than girls from families in which divorce has not occurred. Additionally, adolescents may turn to alcohol or drug use to help cope with the stress of parental divorce. Boys may engage in illegal activities, such as burglary. Suicidal ideation is noted in teenage boys and suicide attempts more often in teenage girls, although this is influenced by whether the teenager is residing with the mother or the father.

Differential Diagnosis

Children who present with reports such as headache, abdominal pain, enuresis, and poor school performance should always be assessed for environmental factors that may be contributing to their symptomatology. When evaluating a child with suspected somatic concerns, it is always appropriate to consider organic etiologies.

Many parents who are undergoing a divorce do not appreciate the effect the divorce is having on their children. They are often caught up in their own personal feelings and are not aware of their children's symptomatology. Additionally, divorcing parents experience a deterioration in their physical and mental well-being, and divorced mothers have an increased rate of illness.

Parents engaged in custody disputes may express concerns that their child is maltreated by the other parent. These concerns may include allegations of sexual abuse, which may require a referral to a physician who specializes in child abuse pediatrics or a child advocacy center (see Chapter 145).

Questions about the family and family resources should be part of any health maintenance visit. A parent may not mention marital discord unless asked specifically. It is important to remember that parental divorce has a significant effect on family resources (see Chapter 141).

Evaluation

Regardless of a child's presenting concern, the focus of the evaluation should be on the interview. Determination of the full extent of the effect of home factors on children's symptomatology may take several visits. It is not appropriate to pursue extensive laboratory tests in search of an organic etiology without first adequately determining what changes are occurring within the household.

History

The medical evaluation of the child experiencing a parental divorce should include a review of the medical history and a discussion with the child of factors of change (Box 149.1). This may help open up a discussion that reveals that the parents are in the process of divorce or that 1 parent has moved out of the household. Specific parental concerns about child maltreatment should be noted in detail and consideration given to consultation with a physician certified in child abuse pediatrics.

Physical Examination

Any symptom or specific report, such as abdominal pain or headache, should also be addressed (see Chapters 125 and 129, respectively). Depression and the risk for suicide should also be evaluated (see Chapter 66). A complete physical examination is usually warranted because the child who is experiencing stress may also develop stress-related medical problems. If concerns exist about sexual abuse, a careful anogenital examination by an experienced examiner is indicated.

Laboratory Tests

Some simple baseline laboratory studies may be warranted, particularly in the child with reports such as abdominal pain or enuresis. These tests may include a complete blood cell count or urinalysis.

Box 149.1. What to Ask

Divorce

- Is anything different about the child's house now?
- What are the current living arrangements?
- Who lives in the house?
- Is this the house in which the child has resided previously?
- Does the child have to move between the residences of each parent?
- How does the family assure that the child has adequate resources (eg, clothes, books, toys) in each household?
- How are things going between the parents?
- Has the child shown any regressive or aggressive behaviors?
- Has the child been eating and sleeping normally?
- How is the child doing in school?

Management

Management of the child whose family is contemplating or undergoing divorce is complex. In addition to managing any somatic symptoms that may be related to the divorce, the physician plays a key role in anticipatory guidance. Children need to understand that they did not cause the divorce and that they will not be able to "cure" it. Physician involvement before parental separation helps. Initially, the physician should advise parents how to talk to children and what to expect in terms of their reaction. It is important for parents to tell children that they are separating from one another and not from the children. As stated previously, parents undergoing a divorce are in so much turmoil that they themselves may not see their children's distress. Additionally, parenting skills may be affected, and routine procedures, such as meals and bedtime, may become disrupted, sporadic, and irregular, and may vary depending on with whom the children are residing.

Box 149.2 summarizes advice given to parents when talking with their children. Parents should discuss who, when, how, where, and what. Ideally, children should be told of impending divorce by both parents with support from the extended family. Although such advice is recommended, studies report that 80% of preschoolers were told by 1 parent. Having both parents tell children is less likely to occur if 1 parent initiated the divorce and the other parent was blindsided by the action.

When to tell depends on children's ages. Younger children should be told a few days before the actual separation, although this too may be unrealistic because plans to separate may spread over a significant period of time (weeks to months). Older children should be told at least several weeks before. The physician should advise parents how to tell. Displays of emotion are permissible. Parents should be encouraged to show their emotions but not to the extent that they appear overwhelmed or uncontrollable.

Box 149.2. Talking to Children About Divorce

Who

- Who tells? Both parents.
- Who is told? Children, extended family, physicians, teachers, neighbors.

When

- Before either parent leaves.
- Age dependent.
  Older children: weeks ahead.
  Younger children: days ahead.

How

- Calmly, with emotional control.

Where

- Privately, in the home.

What

- Stress that children are not to blame; that the divorce is between parents, not between parents and children; it is the parents who cannot get along.
- Explain expected living arrangements.

Who to tell includes not only the children but also the extended family, neighbors, and school, so that the feeling of shame or secrecy are lessened. What to tell involves freeing the children of any blame for the divorce and answering their questions. Parents should be encouraged not to be critical of the other parent, but such advice may be difficult to follow even if the parties involved are not overtly hostile to each other.

It is important for physicians to minimize their involvement in custody disputes; however, if the physician has applicable knowledge, it is acceptable to render an opinion about the parenting skills of both parents. Historically, custody was granted to the mother in 90% of cases, but joint custody (both legal and physical) is now increasing. Questions that physicians should ask themselves when advising about custody include the following: What are the emotional ties between parents and children? Do children indicate a preference for 1 parent? Children may be overwhelmed by feelings of loyalty and be torn if asked to choose 1 parent over the other, which makes this a difficult problem. What is the capacity of each parent to provide emotional and physical support for children? It is important to consider a need for continuity, and it is vital to keep conditions as close as possible to the predivorce situation. Children should not have to move. It is necessary to periodically reassess living arrangements. The pediatrician may also refer parents to community programs that may involve didactic sessions as well as parent groups. One such program, the New Beginnings Program for Divorcing and Separating Families, has been shown to improve mother-child relationships and decrease internalizing behavior in children and externalizing behavior in adolescents.

The physician should be aware of demonstrated benefits of joint custody. Joint custody tends to maintain a parent-child attachment, and children experience a lesser sense of loss. They have more cognitive and social stimulation. Joint custody relieves the burden of single parenthood, and parents who have joint custody are less likely to use children as bargaining tools. Parents themselves are freer to enter into different relationships and are less emotionally dependent on their children. Although the physician should not become involved in monetary issues, concerns related to payment, insurance coverage, and cost of medical care are appropriate to discuss. The physician should consider involving the noncustodial parent in the child's health care. The noncustodial parent should be notified if medical problems occur.

The pediatrician may also be helpful in counseling the noncustodial parent about interacting with children. Unfortunately, contact with noncustodial parents may decrease rapidly after a divorce. Although 25% of children have weekly visits with their noncustodial father, 20% of children see their father only several times a year or not at all. Generally, visitation should reflect previous relationships as closely as possible. The noncustodial parent should be advised not to become a camp counselor who focuses on fun and games but to be an influential figure who helps the child or children meet the challenges of normal living, such as completing homework and doing chores and tasks. It is also important for the noncustodial parent to be consistent. If a meeting is planned, both parents must

show up. Although the parents are no longer married, they can still be co-parents rather than rivals. Rivalry may manifest in ways that include buying more clothes or toys for children, or taking them to costly special events or places. The noncustodial parent should be encouraged to participate in school and sports activities. Multiple modalities, such as e-mail, texting, and video calls can facilitate more frequent communication.

Divorced parents may attribute children's somatic concerns to poor care while under the care of the other parent. Allegations related to abuse, most often sexual abuse, may also arise. These allegations should be taken seriously. An appropriate medical and psychological evaluation is necessary (see Chapter 145). The most difficult situations involve allegations of sexual abuse of preverbal children, in which conclusions may be contingent on the physical findings, which are usually normal or inconclusive.

Issues related to parental dating and remarriage should be addressed at an early stage. Parents should be advised that pediatricians may be a resource in helping families readjust. Remarriage is often a difficult time for children because they experience feelings of rejection secondary to displacement by stepparents. Grandparents may also be a strong source of support and stability, especially if they live close by.

Remarriage may result in a family involving same-sex parents. Many children with gay or lesbian parents have undergone the divorce of their heterosexual parents. In the United States, same-sex marriage has been legal nationwide since 2015. Prior to that ruling by the US Supreme Court, individual states had legalized same-sex marriage, and the 2010 US Census report identified 131,729 married same-sex households. Children may, however, move to families with same-sex parents who are not married. The same report noted 514,735 same-sex unmarried partner households. Studies show that children raised by same-sex parents function similarly to those in heterosexual families.

The pediatrician can also serve as a resource for stepparents. Although stepparents do not have legal rights to consent for medical care of their stepchildren, they should become familiar with the children's medical history. Stepparents grow into their parenting role, and it takes 2 to 7 years for families to become blended. The pediatrician can help families adjust by recommending books or giving referrals to organizations, such as the National Stepfamily Resource Center (www.stepfamilies.info).

Prognosis

The prognosis for children undergoing a parental divorce depends, in large part, on the degree of dysfunction that existed in the family before separation and the ability of the children to communicate their concerns. It takes most children 2 to 3 years to adjust to parental divorce and 3 to 5 years to adjust to a remarriage. Supportive intervention by family, friends, and physicians is key to facilitating the necessary adjustment. For adolescents, a positive belief about parental divorce is a major predictor of their adjustment. Family resilience and hardiness as well as family communication are associated with a good adjustment. Being a child of divorced and remarried parents has been likened to having dual citizenship. The experience is rewarding if the countries are not at war with one another.

Resources for Parents

Clapp G. *Divorce and New Beginnings: A Complete Guide to Recovery, Solo Parenting, Co-Parenting, and Stepfamilies*. 2nd ed. New York, NY: John Wiley & Sons; 2000

Garon RJ, Mandell B. *Talking to Your Children about Separation and Divorce: A Handbook for Parents*. Columbia, MD: Children of Separation and Divorce Center; 1999

Resources for Teenagers

Ricci I. *Mom's House, Dad's House for Kids: Feeling at Home in One Home or Two*. New York, NY: Fireside; 2006

Resources for Children

Brown LK, Brown M. *Dinosaurs Divorce: A Guide for Changing Families*. New York, NY: Little, Brown & Co; 1988

CASE RESOLUTION

The case study reflects that functional somatic symptoms are not uncommon, especially in school-age children of divorced parents. The mother and her daughter should be advised how stressful divorce is for children. A careful medical examination may reassure the mother and daughter about the child's physical well-being. Issues related to custody, financial responsibility, and the need for consistency should all be addressed. The pediatrician also should refer the family to outside agencies, if necessary.

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Wolchik SA, Sandler IN, Jones S, et al. The New Beginnings Program for divorcing and separating families: moving from efficacy to effectiveness. *Fam Court Rev*. 2009;47(3):416–435 PMID: 20160898 https://doi.org/10.1111/j.1744-1617.2009.01265.x

CHAPTER 150

School-Related Violence and Bullying

Tracey Samko, MD, FAAP, and Catherine A. DeRidder, MD, FAAP

CASE STUDY

A mother brings in her 9-year-old son, Alex, who reports recurrent abdominal pain. His pain has become so severe that Alex misses school frequently. He denies any vomiting or diarrhea. His weight has been stable over the past 6 months. Alex's mother reports that lately he seems more withdrawn and passive. He used to be engaged in his schoolwork but now, with his frequent absences, has lost interest in school. His mother says he is often anxious or nervous about new situations.

Questions

1. How does school-related violence, including bullying, affect a child's health and well-being?
2. What is the relationship between bullying and adult criminal behavior?
3. What is cyberbullying?
4. Which children are at risk for being bullied or for becoming a bully?
5. What can the pediatrician do to help address violence in the school, home, and communities?

Violence is defined as an act of aggression that can be physical, sexual, or psychological. Its form, level of severity, and frequency are affected by biological, individual, clinical, intrapersonal, situational, and sociocultural factors. Categorization of violence is also dependent on the relationship of the perpetrator and the perpetrator's target, as well as the age of each party. Intimate partner violence occurs among individuals in an established relationship; child abuse predominantly occurs between an adult and a minor; and bullying usually occurs between peers. School violence occurs at school, at school-related events, in transport to and from school, or on school property. From a developmental perspective, bullying may be the earliest form of violence instigated by children and can progress to intimate partner violence, criminal delinquency, suicide, or homicide in adolescence and adulthood. Although violence may be considered a social issue, it affects the physical and mental health of all involved. The primary care physician has unique opportunities to prevent violence and identify those potentially at risk.

Prevalence and Risk Factors

Suicide and homicide represent the most lethal forms of violence. Suicide and homicide are responsible for more than one-third of deaths among persons age 10 to 24 years in the United States. Approximately 3 million youths are at risk for suicide, with 37% of at-risk individuals attempting suicide (see Chapter 66), and these rates have been steadily increasing since 2005. In 2016, suicide was the second leading cause of death among both 10- to 14-year-olds and 15- to 24-year-olds. It is estimated that approximately 16 youths die each day in the United States from suicide. Homicide is also increasing among children and adolescents. According to the Centers for Disease Control and Prevention, homicide is the fourth leading cause of death for youths 10 to 14 years of age and the third leading cause of death for individuals 15 to 19 years of age in the United States.

In 2014, more than 500,000 individuals younger than 24 years were treated in emergency departments for injuries sustained because of violence. In 2017, nationwide surveys of high school students noted that 23.6% reported being in a physical fight 1 or more times in the 12 preceding months. Sixteen percent reported carrying a weapon, such as a gun, knife, or club, on 1 or more of the 30 days preceding the survey. Furthermore, 6.7% of students reported not going to school on 1 or more days in the 30 days preceding the survey because they felt unsafe at school or on their way to and from school. Bullying was found to be much more prevalent than concern about physical violence, with 19% reporting being bullied on school property and 14.9% reporting being bullied electronically. Although nearly 25% of youth have experienced bullying, only 20% to 30% of those youth ever report it to an adult.

A 2014 meta-analysis of 80 studies found a mean prevalence rate of 35% for traditional bullying and 15% for cyberbullying. Those who reported being a bully or being a target were more likely to carry weapons to school and to be involved in frequent fights. Bullying itself is most common in the middle school years. Boys and girls experience similar rates of bullying. Boys tend to participate in physical and verbal bullying, whereas girls use more verbal and relational bullying, such as rumors and social exclusion.

Risk factors associated with bullying are complex and involve the individual, family, peers, and community (Table 150.1). Children are at risk for being bullied or becoming a bully in situations of power imbalance. This includes physical differences, such as age, size, and strength; as well as popularity; demographic characteristics (eg, member of a majority racial or ethnic group or socioeconomic status); social skills; physical abilities; and access to money, information, or technology. Demonstrated individual risk factors associated with violent behavior include exposure to violence as a witness or target, childhood aggression, antisocial behavior, substance use, depressed mood, and hyperactivity. Community risk factors include high concentrations of poverty and low levels of community participation. Protective factors include academic achievement, parent-family connectedness, and engagement of families and teachers. Targets of bullying are more likely to be children who are considered different from their peers, such as those with obesity; with a developmental delay or learning disability; or who are lesbian, gay, bisexual, transgender, or questioning (LGBTQ).

Bullying and its Consequences

Bullying is defined as repeated acts of verbal or physical intimidation, coercion, and aggression. An imbalance of power exists, with the more powerful attacking the less powerful, whether because of physical size, social power, or access to money/information. Bullying occurs in an environment that supports the behavior. Participants include the bully, the target, and the bystander. The bully is often an aggressive individual who uses violence to dominate others. In contrast with common perception, bullies do not have poor self-esteem but rather have a strong desire to control others. The target may be more passive and anxious. This individual is often less secure than his, her, or their peers and may be lonely, playing alone at school. When the target is attacked by a bully, the target usually withdraws rather than retaliates. A minority of youth may be classified as a bully-target or a provocative target. These individuals are anxious and aggressive; although they are primarily targets of bullying, they may provoke the bully.

Different forms of bullying exist. *Direct bullying* includes physical or verbal bullying. *Physical bullying* can involve hitting or kicking, whereas *verbal bullying* can involve spreading rumors and social exclusion. *Cyberbullying* can include bullying via email, social networks, or texting. The bully who uses cyberbullying can remain anonymous and send aggressive messages to many people. Cyberbullying frequently occurs in a public forum in which it can be seen and/or shared both by acquaintances and strangers as well as become part of the public record, where it can be accessed in the future. Because the bullying occurs online, it may go unnoticed by authority figures, is frequently anonymous, and can be difficult to track.

Bullying predominantly occurs in unstructured school environments, such as during recess, at lunch, on the way to or from school, in hallways, or on the bus. Children often do not report bullying to adults for fear of retaliation by the bully and the concern of disbelief by the adult. Despite exposure to high-profile school mass tragedies associated with bullying, many parents, teachers, and health professionals still believe bullying to be a normal behavior of children. Studies demonstrate that adults underestimate the prevalence of bullying events compared with student reports.

Bullying affects the physical and mental health of all involved. Fear and anxiety about the school environment is most common. Other clinical signs of bullying include bed-wetting, headaches, sleeping problems, abdominal pain, poor appetite, and feelings of tension or tiredness. This can progress to avoidance of school; academic problems, including lower academic achievement; and higher dropout rates. Of further concern, bullying can result in low self-esteem, depression, and suicide. Although a direct connection between childhood violence and adult outcomes has not been clearly established, temperament, social skills, biologic factors, timing (transient vs chronic), presence or absence of support by authority figures, and comorbid psychiatric conditions all likely play a role.

Six percent of adults in the United States report a lifetime history of bullying. In adulthood, higher rates of depression and poor self-esteem exist among individuals with a history of being bullied.

Table 150.1. Risk Factors Associated With Bullying

Risk Factor Type	*Target*	*Bully*
Individual	Physical traits different from peers, especially obesity Chronic illnesses Behavioral or emotional problems Sexual orientation (LGBTQ) Physical or learning disabilities	Poor academic achievement Behavioral or emotional problems Involvement with drugs, alcohol, or tobacco Criminal involvement
Family	Abuse (physical, sexual, or psychological) Witness to violence Poor family functioning	Abuse (physical, sexual, or psychological) Witness to violence Poor family functioning
Social environmental	Social rejection by peers Socioeconomic disadvantage Low commitment to school and school failure Inner-city upbringing	Association with delinquent peers/peer pressure Socioeconomic disadvantage Low commitment to school and school failure Inner-city upbringing

Abbreviation: LGBTQ, lesbian, gay, bisexual, transgender, questioning.

Adapted with permission from Waseem M, Ryan M, Foster CB, Peterson J. Assessment and management of bullied children in the emergency department. *Pediatr Emerg Care.* 2013;29(3):389–398.

Strong associations in adolescence and early adulthood have been made between bullying, suicide, and murder. The child who was targeted may react later in life with self-destructive acts or lethal retaliation.

Many of the recent killing sprees in the United States were committed by individuals who as children felt they were targeted. A review of 37 mass school shootings found more than two-thirds of perpetrators felt they had been persecuted, bullied, threatened, or attacked; often, they were acting out of revenge. Regardless of the scale, the rate of gun violence in the United States is higher than that of similar high-income countries.

A cohort study of 1,420 individuals age 9 to 26 years in western North Carolina found that targets of bullying had significantly higher likelihood of poor health, wealth, and social-relationship outcomes compared with children who were not bullied. Bullies who were not bullied themselves were not at increased risk for adverse outcomes as an adult when other environmental factors and childhood psychiatric disorders were controlled.

However, studies have found that boys who were bullies in middle school had at least 1 criminal conviction by age 24 years, and 35% to 40% had 3 or more convictions by age 24 years compared with 10% among a control group of boys who were not involved in bullying. Longitudinal studies report that bullies and bully-targets go on to more criminal activity than their counterparts. Those who are chronically bullied have worse outcomes than those who are bullied transiently. One study of Finnish boys reported 9% being bullies in childhood. These same individuals accounted for 33% of criminal activity in the study. Bullies were more likely to commit occasional infractions, whereas bully-targets were more likely to commit repeat offenses.

Bystanders are also affected, because bullying distracts from the learning environment. Furthermore, bystanders develop strategies to avoid being bullied themselves, including avoiding the restroom and staying home from school. One study reported that 1 in 5 secondary schoolchildren avoid restrooms out of fear at school. Another study stated that 7% of eighth graders stay home at least 1 day a month out of fear of other students.

Role of the Primary Care Physician

Assessment

Childhood bullying is a complex abusive behavior with demonstrated serious consequences. The physician is uniquely qualified to identify at-risk individuals, screen for psychiatric comorbidities associated with bullying, counsel families, and advocate for school-based interventions. Because bullies and targets commonly will not identify themselves as such, the physician needs a systematic approach to screen for this early form of violence. Integrating screening during anticipatory guidance may be optimal for toddlers and school-age children, whereas assessing risk factors at well- and acute-care visits may be necessary for adolescents.

Multiple instruments have been used in a research setting for identifying bullying or associated internalizing or externalizing symptoms, but they have not been widely implemented in the primary care setting. Screening younger patients requires conversations with the child and family members. The American Academy of Pediatrics developed Connected Kids: Safe, Strong, Secure, which can be integrated into Bright Futures for well-child care visits. This violence prevention program focuses on screening for risk, preventive education, and links to counseling and treatment resources. When talking directly with adolescents, the use of the psychosocial interview HEADSS (home, education and employment, activities, drugs, sexuality, and suicide/depression) may be useful in screening for high-risk behaviors and risk factors for violence (see Chapter 4).

When questioning a family about bullying, the physician must keep in mind that children often do not tell a parent that bullying occurred. When a parent is told about bullying, the parent may consider the situation to be normal behavior for young people and dismiss the event.

After bullying involvement is suspected, the physician can ask follow-up questions to further characterize the involvement and obtain more details (Box 150.1).

Prevention

Prevention efforts must be focused on the individual, family, and community. In early childhood, the parent can model for the child appropriate social interaction, how to resolve conflict, and how to manage frustration and anger. School-wide bullying prevention programs are effective and should be advocated. One example is the Olweus Bullying Prevention Program (www.violencepreventionworks.org), which focuses on caregivers and schools showing positive interest in students, setting firm limits for unacceptable behavior, using consistent nonphysical consequences when rules are broken, and acting as positive role models to ultimately change social and behavioral norms. For older children and adolescents, identifying psychiatric symptoms and providing the appropriate intervention may

Box 150.1. What to Ask

Bully

- How often do you bully others?
- How long have you bullied others?
- Where do you bully others (eg, school, sports, home, neighborhood)?
- How do you bully others (eg, hitting, insults, gossiping, text messaging, social networks)?
- How do you think the kids you bully feel?
- How does bullying make you feel?

Target

- Have you been bullied? If so, how often have you experienced bullying?
- How long have you experienced being bullied?
- Where are you bullied (eg, school, sports, home, neighborhood)?
- How are you bullied (eg, hitting, insults, gossiping, text messaging, social networks)?
- How do you feel when you are the target of bullying?

Adapted with permission from Lamb J, Pepler DJ, Craig W. Approach to bullying and victimization. *Can Fam Physician.* 2009;55(4):356–360.

prevent more serious violent behavior. At the individual level, physicians and parents can counsel children who are bullies or targets about appropriate behaviors (Box 150.2).

The authors of a randomized controlled study published in 2004 demonstrated the effectiveness of identifying at-risk youth age 7 to 15 years in a primary care setting and providing a family-level intervention to reduce violent behavior and injuries among youth. Families who received the telephone-based intervention focusing on positive parenting reported decreased parent-reported bullying, physical fighting, fight-related injuries requiring medical care, and child-reported bullying.

Some strategies should be avoided, including zero tolerance policies, which can disincentivize reporting; conflict resolution/mediation, which can give the impression that both the target and the bully are partly at fault; and group therapy, which may reinforce power dynamics and bully behaviors among the participants.

The US Department of Health and Human Services developed a resource kit on bullying, which is available at https://www.hhs.gov/ash/oah/adolescent-development/healthy-relationships/bullying/index.html. Printed resources are available for parents and teachers. PACER's National Bullying Prevention Center (www.pacer.org/bullying/) also has digital-based resources for parents, educators, teenagers, and youth. For LGBTQ youth, the physician can recommend GLSEN (formerly known as the Gay, Lesbian & Straight Education Network; www.glsen.org/) and the It Gets Better Project (https://itgetsbetter.org/).

The National Suicide Prevention Lifeline is available at www.suicidepreventionlifeline.org and 1-800-273-TALK (8255). This lifeline provides 24/7 crisis counseling and mental health resources. For LGBTQ youth, The Trevor Project offers a 24/7 crisis hotline at 1-866-488-7386 and www.thetrevorproject.org/.

The physician serves a vital role in youth violence prevention (Box 150.3). Prevention begins early in a child's development by providing positive reinforcement of appropriate pro-social behavior. Bullying is an early form of aggression. Bullying may seem harmless, but longitudinal studies as well as analysis of mass school shootings demonstrate the large effect aggression early in life can have on the future well-being of children, adolescents, and adults. Successful interventions require cooperation by parents, teachers, students, and health professionals. At a community level, pediatricians can advocate for incorporation of school-wide bullying awareness campaigns, educate themselves and others about violence prevention, contribute to ongoing research, and promote awareness of violence prevention/intervention strategies at local and state levels.

Box 150.2. The Role of the Physician in Counseling Bullies and Targets

- Be vigilant for signs and symptoms of bullying and other psychosocial trauma and distress in children and adolescents.
- Increase awareness of the social and mental health consequences of bullying and other aggressive behaviors.
- Screen for psychiatric comorbidities in at-risk youth and provide appropriate referrals for treatment for affected youth.
- Counsel affected youth and their families on effective intervention programs and coping strategies.
- Advocate for family, school, and community programs and services for targets and perpetrators of bullying and other forms of violence and aggression.

Box 150.3. Individual-Level Prevention Strategies

Advice for Targets of Bullying

- Resist reacting to the bully; hold your frustration and anger.
- Walk away from the situation; ignore the bullying.
- Avoid retaliation or bullying back.
- Tell an adult.
- Talk about the bullying event with your family.
- Assess each bullying situation individually.
- When possible, use a buddy system at school and while traveling to and from school.
- Develop friendships by joining social organizations.

Management of Bullies

- Reinforce that bullying is a serious problem.
- Set limits and provide consequences for acts of aggression.
- Emphasize tolerance for people's differences; everyone deserves respect.
- Determine whether friends are also involved in bullying; encourage others to report bullying behavior.
- Provide positive reinforcement for appropriate behavior.
- Work closely with teachers and school staff on behavior modification.
- Emphasize it is the behavior that is not acceptable, not the individual as a whole.

CASE RESOLUTION

Targets of bullying often present with psychosomatic symptoms, such as headache or abdominal pain. After organic etiologies have been ruled out, further questioning should focus on psychosocial stresses. Alex's abdominal pain is worse in the morning before going to school. When asked specifically about bullying, Alex states that a few of his classmates tease him and rough him up each day on his way to school. In the past few weeks, they have been sending him text messages about how they are going to haze him the next day. Alex has not told anyone about the experience because he thought he would be viewed as a coward. Alex shares that he would rather avoid going to school than face potential bullying.

The physician needs to assure Alex that it is not his fault that he is a target of bullying. Prevention should include interventions at the individual, family, and school level. Alex should walk away from the conflict when possible and feel comfortable about reporting the event to school staff. He may want to find a friend with whom he can walk to school. His family needs to understand that bullying is not a normal behavior of childhood. He should be encouraged to talk about bullying events and work with his family to identify solutions. The school should be notified of the event and encouraged to promote a non-bullying school environment.

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CHAPTER 151

Intimate Partner Violence

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CASE STUDY

A 6-year-old boy is brought in by his mother for an annual well-child visit. He sits quietly as his mother reports no significant medical history. His medical records reflect that at his last visit he was talkative, doing well in school, and enjoyed playing baseball. As you speak with his mother, she seems reticent and does not spontaneously offer information. You determine that the boy's school performance has declined significantly over the past year and that he no longer wants to play baseball.

On physical examination, the boy has linear ecchymoses over his buttocks, and you notice bilateral areas of bruising on his mother's upper arms. When you ask about the marks, she becomes tearful. You ask her if she would like to speak privately with you.

Questions

1. How often does child abuse and intimate partner violence co-occur?
2. What are potential strategies to screen for intimate partner violence?
3. What are common clinical presentations of victims of intimate partner violence and children exposed to intimate partner violence?
4. What are the long-term consequences of intimate partner violence on children?
5. What are key factors in determining the risk to a target of intimate partner violence?

Although several definitions of *intimate partner violence* (IPV) exist, the Centers for Disease Control and Prevention has defined it as a pattern of behavior that includes physical violence, sexual violence, stalking, and psychological aggression. It is perpetrated by an individual who is or was involved in an intimate relationship with an adult or adolescent, and the pattern of assaultive and coercive behaviors is meant to establish control over the other partner. This may include approaches such as social isolation, deprivation, and intimidation. Intimate partner violence is not only associated with negative physical and mental health outcomes for the victim but is also associated with negative mental health outcomes for children in the home. Childhood exposure to IPV is considered to have occurred when a child sees, hears, or observes the effects of verbal or physical assaults between partners. Intimate partner violence is also associated with an increased incidence of child abuse in the home.

Epidemiology

Intimate partner violence affects both sexes and occurs in all ethnic, socioeconomic, sexual orientation, and religious groups. Approximately 8.5 million women and 4 million men in the United States report experiencing physical violence, rape, or stalking from an intimate partner during their lifetime. Of adolescents who date, 12% of girls and 7% of boys have experienced physical violence in their dating relationship in the prior 12 months. In 2007, 14% of homicides nationwide were the result of IPV, and most of these victims were female. Although both men and women fall victim to IPV, women are more likely to sustain life-threatening injuries, resulting in an increasing disparity between victimization rates with increased severity of physical assault. The annual financial cost of IPV to society has been estimated at $8.3 billion, including medical and mental health costs as well as the indirect cost of lost productivity. In total, victims lose millions of days of paid work time annually.

Although no uniform profile exists of a victim or perpetrator of IPV, risk factors for victimization include a personal history of maltreatment as a child, adolescent or young adult age, disparity of status (eg, educational, professional) between partners, and high level of dependence of 1 partner on another. Batterers have also been found to frequently have a history of emotional or physical maltreatment as a child, a history of substance abuse, very low levels of self-esteem, and difficulty identifying and expressing emotion.

It is estimated that up to 15 million children in the United States are exposed to IPV in their homes annually, and these children are at risk of victimization themselves. They are almost 5 times more likely than unexposed children to sustain physical abuse and 2.5 times more likely to be victims of sexual abuse.

Clinical Presentation

Adult victims of IPV may present for medical care for themselves or may present for care of their children for issues related to the violence. Approximately one-third of victims injured in an assault by a partner seek medical care for their injuries. Although these

injuries vary in severity, skin injuries are most common. Injury can occur on any part of the body; however, injury to the head, neck, and face has been particularly associated with IPV.

Many victims present to primary care physicians and emergency departments, and only a fraction are correctly identified as suffering from IPV. A recent report noted that only 28% of abused women who sought care frequently (≥7 times) were ever identified as victims of IPV. Barriers to diagnosis are patient and physician based. A patient may not disclose the abuse because of fears of social, financial, or legal repercussions; concerns for safety based on prior threats from the abuser; feeling ashamed at being a victim; and inability to trust that others can help. The patient does not appreciate that violence frequently escalates. Often the patient fears an investigation by child protective services and loss of custody of any children in the process. The patient may fabricate a story (eg, a fall) to explain the injuries, thereby discouraging the physician from further inquiry. Even in the absence of a story, the physician may avoid inquiring about the injuries, citing time constraints and lack of knowledge to effectively respond if a disclosure is made.

A parent or guardian may also seek care for any children who manifest effects of the trauma, altered stress physiology, and disrupted caregiver attachment (Box 151.1). Children exposed to IPV are more likely than their peers to be anxious, fearful, and hypervigilant and have difficulty with aggression and peer relationships. Adolescents are more likely to have school failure, substance abuse difficulties, high-risk sexual behaviors, and violent dating relationships. As they progress to adulthood, these children are at increased risk for mental health disorders and substance abuse. The Adverse Childhood Experiences Study enumerates multiple negative overall physical and mental health consequences in adults exposed to IPV as children (see Chapter 142).

Pathophysiology

The prevalent dynamic in relationships with IPV is the need by 1 partner to dominate or have power over the other. Often, this characteristic is interpreted as devotion early in a relationship, but an abuser eventually isolates the victim socially and financially. Ultimately, the violence includes a physical or sexual component as well as a psychological one. The psychological component, which typically precedes any physical violence, includes threats, humiliation, and intimidation and can be the most difficult to treat.

The cycle of violence between intimate partners is chronic and cyclic in nature, with 3 phases. The first phase is the tension-building phase, in which the abuser uses verbal, emotional, and physical threats. The next phase is the violent episode, which includes some combination of physical, sexual, emotional, and psychological assault. The final phase is the honeymoon phase, in which the abuser apologizes and assures the victim that it will not happen again, and re-bonding occurs. These phases escalate over time as the violence becomes more frequent and more severe and the honeymoon phase shortens. At least 50% of women who suffer sexual IPV report multiple rapes, and two-thirds of men and women with physical violence report multiple episodes of assault as well. The violence can also continue after the relationship has ended, and this most commonly manifests as stalking of the victim by the abuser. The violence also becomes intergenerational, because children exposed to IPV are at increased risk for victimization and perpetration of violence in their future intimate relationships.

Particular circumstances exist in which IPV victims are at even higher risk of harm. Threats from the perpetrator to harm or kill the victim or another person, the use of drugs or alcohol at the time of the violent episode, and the use of a weapon are all associated with an increased risk of injury. Approximately 4% to 8% of women report having experienced IPV during a pregnancy. It has been hypothesized that this is a time of increased stress as well as a time when a woman's attention may be diverted from her partner, thus placing her at increased risk for harm. Victims are also at increased risk of injury or death at the time they report the abuse or attempt to leave the relationship. In comparison with the systems in place for children, no protective service agencies with mandates to protect these adult victims exist, and as a result, disclosure of IPV may not occur unless the victim feels that she, he, or they has a plan for escape.

Box 151.1. Signs and Symptoms of Childhood Exposure to Intimate Partner Violence

- Depression
- Anxiety
- Somatization
- Attention-deficit/hyperactivity disorder
- Aggression
- Developmental delay
- Low self-esteem
- Hypervigilance
- Poor academic performance or truancy
- Antisocial or delinquent behaviors

Differential Diagnosis

Adult or adolescent victims of IPV often present with vague symptoms, and women who have been abused are 3 times more likely than women who have not been abused to present with gynecologic complaints, such as recurrent sexually transmitted infections, vaginal bleeding, or chronic pelvic pain. These victims may also present with nonspecific symptoms of sleeping difficulties, appetite changes, weight loss, chronic pain, or syncope. They are 3 times more likely to experience depression and 4 times more likely to experience posttraumatic stress disorder (PTSD) than non-abused women and may present to their physician with symptoms of anxiety or after a suicide attempt. Other symptoms reflect conditions associated with stress, such as irritable bowel syndrome, headaches, or temporomandibular joint disorder. The pregnant victim may present with vaginal bleeding, preterm labor, placental abruption, or fetal distress. The most common adverse birth outcome attributed to IPV during pregnancy is low birth weight of the neonate.

Mental health manifestations of childhood exposure to IPV may vary depending on the developmental stage of the child; however, these children may present with developmental delay, low self-esteem, symptoms of PTSD and hypervigilance, poor academic performance or truancy, or antisocial behavior. Exposed children also have significantly more internalizing disorders (eg, depression, anxiety, somatization) and externalizing disorders (eg, attention-deficit/hyperactivity disorder, aggression) than nonexposed children.

Children in the home may also sustain direct physical trauma as the result of being held in a parent's arms during an episode of violence or in an effort to intervene and protect a parent during a violent episode. The children may also be direct targets of the violence and present with head, skin, skeletal, or abdominal findings caused by physical abuse (see Chapter 144).

Box 151.2. Risk Factors for Intimate Partner Violence

- History of childhood abuse
- Adolescent or young adult age
- Disparity in professional or educational status of partners
- Geographic or cultural isolation
- Dependency on partner because of chronic illness or disability
- Pregnancy
- Depression
- Anxiety
- Frequent physical injury
- Substance abuse
- Poor compliance with medical care

Evaluation

History

Many victims of IPV do not freely offer information about the violence occurring in their relationships, even if they present with overt injuries. Screening for IPV in medical settings is cited as the optimal approach and is an area of continued research. Several different screening tools have been used clinically, but no standard screening tool has yet been established. Proposed approaches in the primary care or emergency department environment have included universal screening of all women and targeted screening of women with high-risk signs and risk factors. Although each approach has its proponents, a 2013 US Preventive Services Task Force statement recommended that physicians screen all women of childbearing age. Universal screening may detect increased numbers of cases of IPV and "open the door" to effective intervention, but it remains unknown whether improved social, physical, or mental health outcomes have been achieved with this approach. Critics of universal screening argue that forcing the issue before a woman is psychologically and logistically ready to leave the situation may put her at increased risk of harm and decreased likelihood of success. However, a 2015 Cochrane Review found no evidence of harm resulting from IPV screening. The universal screening approach has not typically addressed the population of male victims of IPV.

Alternatively, targeted screening is performed in some medical settings on patients who present with risk factors for IPV (Box 151.2). Studies have shown that self-administered, written screening tools are more sensitive and are preferred by victims over verbal questioning.

Because IPV has been shown to have a direct effect on the health and well-being of children in the home, the pediatric medical setting is a potential site for IPV screening to occur. Targeted screening practices may focus on families of children with anxiety, depression, or somatization or in situations in which child abuse is suspected. Surveys of mothers generally support IPV screening in the pediatric office setting, and women who have been abused are more likely to seek medical care for their children than for themselves. Sensitivity to whether children should witness discussions of positive screening questions is necessary, because older children may react to or repeat portions of an overheard conversation, ultimately placing the victim, their mother, at increased risk of harm.

Physical Examination

Caregiver Injuries

Although blunt trauma from a hand or fist is the most common scenario for the abused partner, IPV can result in injuries from penetrating trauma. Injury can occur on any part of a victim's body; however, studies have shown that trauma to the head, neck, and face is most specific for IPV as the etiology compared with other traumatic events. Findings may also include bruising of the bilateral upper arms from being grabbed and patterned injury from being hit with an object. Strangulation may result in bruising or abrasions on the neck, facial petechiae, or subconjunctival hemorrhage.

Child Injuries

Children in the home in which IPV is occurring are at increased risk of physical abuse, and a complete unclothed physical examination should be performed to look for evidence of skin, head, skeletal, or abdominal trauma. Accidental injuries typically result in cutaneous bruises over bony prominences, such as knees and elbows, anterior shins, and the forehead. Unusual areas for accidental injury include the neck, ears, cheeks, medial thighs, and genital area. If physical abuse is suspected, additional radiographic imaging and an ophthalmologic examination may be indicated (see Chapter 144).

Management

The response to any disclosure of IPV should be supportive and focus on a safety assessment to determine the severity and immediacy of danger (Box 151.3). This should include an assessment of the pattern of escalating violence, availability of weapons to the abuser, and comfort level of the victim to return home. More imminent danger necessitates the creation of an emergent safety plan, and social work colleagues or professionals from an IPV shelter, hotline, or advocacy organization can assist with this. It is important for the physician to remain sensitive to the fact that leaving an abusive home is disruptive to the daily lives of the adult and child victims and may be a difficult step to take.

Box 151.3. Components of Safety Assessment

- Is the violence escalating?
- How severe has the violence been in the past?
- Is the victim comfortable returning home?
- Is child abuse occurring?
- Are weapons available to the perpetrator?
- Does the perpetrator have substance abuse issues or a mental health disorder?
- Does the victim have a social support network?

If immediate safety is of less concern, a victim may opt to take more time in creating a safety plan for leaving. This may include things such as collecting money, car keys, house keys, and important documents; asking neighbors to contact police if violence is overheard in the home; establishing a code that the victim can use to communicate to others that violence is occurring and that prompts the contact to take certain action on use of the code; and disarming or removing weapons from the home.

Although all states require that medical professionals report cases of suspected child abuse and neglect to child protective agencies, mandated reporting statutes for IPV and child exposure to IPV vary. State statutes fall into the following general categories with respect to IPV: requirement to report injuries caused by weapons, requirement to report injuries resulting from a crime, requirement to report IPV, and no mandatory reporting law. For those states with no mandatory reporting requirement, factors that may influence a physician's decision to report may include the potential for danger, the caregiver's ability to plan for safety, a victim's level of connection to family or community support, and the degree of suspicion that a child's exposure to IPV constitutes emotional abuse. Online resources, such as the *Compendium of State Statutes and Policies on Domestic Violence and Health Care,* published by the Family Violence Prevention Fund in 2010, can assist with the determination of local state laws on mandatory reporting of IPV. Any suspicion of child abuse should be reported to child protective services, regardless whether IPV is being reported as well. If child abuse and IPV are co-occurring, it is important to note this in the child abuse report so that appropriate measures can be taken in the child protection response. Any child with a history of exposure to IPV should also be referred for trauma-focused mental health services.

Prognosis

Direct victimization from IPV and childhood exposure to IPV are associated with increased risk of adult morbidities. Women who have experienced interpersonal violence are at risk for depression, anxiety, PTSD, and becoming victims of human trafficking, and they are 15 times more likely to abuse alcohol and 9 times more likely to abuse drugs than their peers who do not experience IPV. Childhood exposure to IPV is associated with an increased risk of adult morbidities, including substance abuse disorders, obesity, physical inactivity, depression, and suicide attempts. This is of particular concern because of the limited availability and often limited recognition of the importance of mental health resources in addressing the psychological effect of IPV in both adults and children.

For those women who do disclose the abuse and are referred to advocacy programs, preliminary data indicate that intensive programs may have a beneficial effect on reducing physical violence for several years. For other intervention strategies, the research is often limited and does not yet provide sound evidence of positive effects on physical, emotional, and quality-of-life outcomes. Further research is necessary to determine what components of the programs and what intensity and time frame of involvement are most beneficial in different clinical scenarios.

Although many IPV shelters and advocacy organizations have legal assistance available to victims, most victims do not obtain temporary restraining orders. Of those who do, in approximately two-thirds of cases the orders are violated by the abuser. Most cases are not prosecuted, and for those cases that do progress in the legal system, courts often struggle with how to address the IPV issues in the child custody and family treatment plans. Although multiple models of treatment programs exist for perpetrators of IPV, the evidence for sustained change in behavior is unclear. Barriers to behavior change include substance abuse, mental health issues, and relationship dynamics. Further research is necessary to modify treatment approaches to reduce recidivism.

Prevention

Prevention efforts may be primary, secondary, or tertiary. In this setting, primary prevention includes attempts to change social norms of violence and acts at the level of the individual, relationship, or community. Current efforts in primary prevention include attempts to break the generational cycle by studying and supporting resilience factors in those who do not perpetuate violence after childhood exposure, the development of safe dating programs to reduce adolescent dating violence, the creation of peer empowerment programs for adolescents and young adults to enhance their ability to identify and intervene in IPV that they witness, and the development of family-based interventions to enhance nonviolent communication skills.

Secondary prevention includes early detection of IPV, and a significant amount of research is underway on screening practices in the medical setting. Tertiary prevention is the attempt to prevent death and disability in families in which IPV occurs.

Sound research on IPV prevention remains a work in progress. Much of the current research has had methodological challenges, and many prevention strategies are not yet validated by sound evidence of benefit. Additionally, traditional thinking has been that most abusers are male and most victims are female, and prevention programs were built on this premise. Recent data, however, suggest that females also instigate IPV, so the subtleties of the patterns of violence of men versus women and how best to prevent them is a new area for growth and understanding.

CASE RESOLUTION

When alone with you, the mother reports that the boy's bruising occurred after her boyfriend hit him with a belt and that her marks occurred when the boyfriend was drunk and angry about the dinner she had prepared. She has contemplated leaving the relationship but is financially dependent on her boyfriend and pregnant with his child. He has threatened to harm her son if she leaves. She is afraid to return home but is not sure what to do.

You contact a social worker who assists in referring the mother and child to an IPV shelter and an IPV advocacy group. The social worker and the agencies work on an immediate safety plan while the mother and child wait in the office. As a mandated reporter of child abuse, you contact the child abuse hotline. The social worker assists you with the requirements in your state to report IPV or childhood exposure to IPV. The mother should be advised that a child abuse report was initiated, and child protective authorities should also be made aware that IPV and child abuse are co-occurring in this family.

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PART 15

Chronic Diseases of Childhood and Adolescence

CHAPTER 152

Cancer in Children

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CASE STUDY

A 10-year-old boy has a history of intermittent fevers of 39.0°C (102.2°F) for 1 month. For 2 days, he has experienced increasing shortness of breath with rapid respirations. His face is dusky and plethoric, and the veins in his neck are prominent. He has bilaterally enlarged cervical lymph nodes. The remainder of the examination is normal.

His blood cell count is normal, but the erythrocyte sedimentation rate is 110 mm/h. A chest radiograph reveals a large mediastinal mass.

Questions

1. What signs and symptoms are associated with malignant conditions in children?
2. What oncologic emergencies require immediate attention?
3. What factors correlate with the manifestation of cancer in children?
4. What is the role of the primary care physician in the care of the child diagnosed with cancer?

Epidemiology

Childhood cancer is rare. Approximately 12,400 children and adolescents younger than 20 years are diagnosed with cancer each year in the United States. The likelihood of a child developing cancer before the age of 20 years is 1 in 300 for males and 1 in 333 for females. The overall incidence of childhood cancer has been slowly increasing since the mid-1970s, but death rates have declined dramatically for most childhood cancers and survival rates have improved markedly since the 1970s. Cancer remains the leading disease-related cause of death in children younger than 15 years, however. The prevalence of cancer is higher in children younger than 5 years and in children between the ages of 15 and 19 years. Acute hematologic malignancies, sarcomas, and embryonic neoplasms with fewer mutations are more typical in the pediatric age group compared with adults, who develop genetically more complex cancers and carcinomas of epithelial origin. Acute leukemia is the most common childhood cancer, followed by brain tumors, lymphomas, neuroblastoma, Wilms tumor (ie, nephroblastoma), and other less common pediatric solid tumors (Figure 152.1).

Environmental factors, genetic predisposition, and developmental processes may all play a role in influencing the cancer risk of a child. Case-control epidemiology studies looking for the causes of pediatric cancer have evaluated foods, prenatal exposures of parents and affected offspring, electromagnetic fields, radon, and various other environmental factors with no conclusive evidence of causality to date. Although many environmental factors are known to induce carcinogenesis, current evidence does not support a major causative role for exogenous factors in childhood cancer. Most childhood cancers result from aberrations in early developmental processes. Some known risk factors for selected childhood cancers include infectious agents, such as Epstein-Barr virus (eg, B-cell lymphomas, Hodgkin lymphoma, nasopharyngeal carcinoma), HIV (eg, B-cell lymphomas, Kaposi sarcoma, leiomyosarcoma), and hepatitis B and C (eg, hepatocellular carcinoma); ionizing radiation (eg, leukemia, osteosarcoma, brain tumors); chemotherapeutic agents (eg, leukemia, osteosarcoma); immunodeficiency (eg, non-Hodgkin lymphoma); and genetic conditions. Approximately 4% to 10% of childhood cancer results from known inherited genetic mutations that result in a cancer predisposition. Children with trisomy 21 syndrome (ie, Down syndrome) have an increased risk of leukemia (eg, lymphoid and myeloid). Beckwith-Wiedemann syndrome is associated with an increased risk for hepatoblastoma, Wilms tumor, rhabdomyosarcoma, and neuroblastoma and warrants appropriate surveillance screening. Inheritance of mutations in tumor suppressor genes, such as the retinoblastoma gene or the p53 gene, predispose affected children in families with these mutations (eg, Li-Fraumeni syndrome) to particular malignancies at a greater frequency and an earlier age than in unaffected individuals. Some children with tuberous sclerosis or neurofibromatosis 1 will develop multiple types of brain tumors.

Clinical Presentation

Signs and symptoms of childhood cancer are varied, are often nonspecific initially, and can mimic many common pediatric conditions (Table 152.1). Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for 80% of pediatric leukemia cases. Acute myeloid leukemia accounts for the remaining 15% to 20% of cases. The child with acute leukemia presents with signs and symptoms that reflect leukemic infiltration of the bone marrow and extramedullary locations. Presentation with generalized bone pain and signs and symptoms related to pancytopenia (ie, fever, fatigue, pallor, bleeding, bruising, infections) is common. Disseminated intravascular coagulation is more characteristic of acute myeloid leukemia, especially acute promyelocytic leukemia.

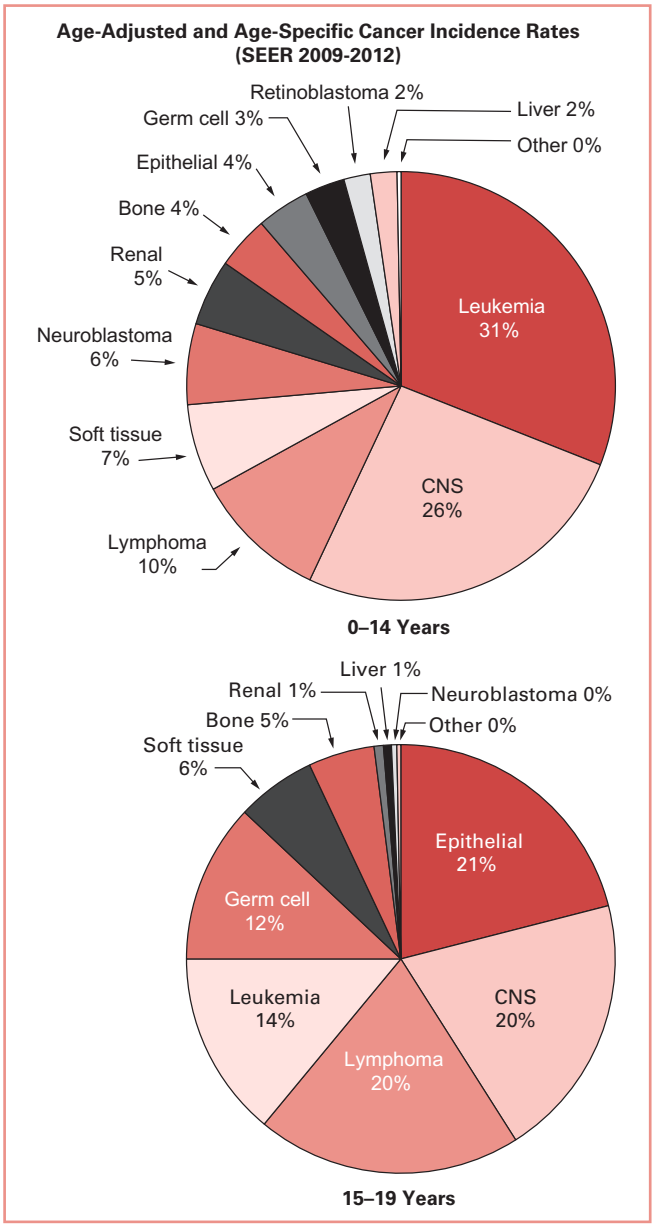

Figure 152.1. Cancer incidence rates for patients aged 0 through 14 years and 15 through 19 years in the Surveillance, Epidemiology, and End Results (SEER) Program from 2009 through 2012 by International Classification of Childhood Cancer group and subgroup and age at diagnosis, including myelodysplastic syndrome and group III benign brain/central nervous system tumors for all races for males and females. Incidence rates are age-adjusted and age-specific and are shown for leukemia, lymphoma, central nervous system (CNS) tumors, neuroblastoma, retinoblastoma, renal tumors, hepatic tumors, bone tumors, soft tissue tumors, germ cell tumors, carcinomas and melanomas, and other cancers. Retinoblastoma occurs infrequently in adolescents aged 15 through 19 years. Reprinted from Unusual Cancers of Childhood Treatment (PDQ®)–Health Professional Version. National Cancer Institute website. https://www.cancer.gov/types/childhood-cancers/hp/unusual-cancers-childhood-pdq#_105. Accessed November 26, 2019.

Leukemic infiltration of extramedullary sites can result in hepatosplenomegaly, lymphadenopathy, *chloroma* (ie, a green-colored tumor of myeloid cells), central nervous system (CNS), and sometimes testicular involvement. The child with high white blood cell counts at presentation, as in leukocytosis, can present with signs and symptoms of leukostasis typically involving the lung or brain. Tumor lysis syndrome can occur spontaneously or with the initiation of intravenous (IV) hydration or chemotherapy. Tumor lysis syndrome occurs as a result of breakdown of leukemic blasts that results in the release of metabolic by-products. It is characterized by a metabolic triad of hyperuricemia, hyperkalemia, and hyperphosphatemia, which places a child at risk for renal dysfunction or failure secondary to precipitation of urate or calcium phosphate crystals within the renal tubules. Involvement of the CNS by leukemia can result in signs of increased intracranial pressure (ICP), such as headache, vomiting, hypertension, seizures, and cranial neuropathies.

T-cell ALL or T-cell lymphoblastic lymphoma can present with a large anterior mediastinal mass and symptoms related to compression by the mediastinal mass on the trachea and blockage of venous return and lymphatic drainage, that is, *superior vena cava syndrome* (SVC syndrome). The child with SVC syndrome can present with wheezing, dyspnea, dysphagia, plethora, and cyanosis. Pleural or pericardial effusions may also be present. Superior vena cava syndrome can rapidly progress and constitutes a true oncologic emergency that requires prompt intervention.

Lymphomas in children can be divided pathologically into Hodgkin or non-Hodgkin lymphoma. The child with Hodgkin lymphoma typically has a prolonged history (often ≥2–3 months' duration) of painless enlarging cervical or supraclavicular lymphadenopathy. Affected lymph nodes can be firm, immobile, rubbery, and nontender. In two-thirds of cases, mediastinal adenopathy may be present, resulting in cough or wheeze. Constitutional symptoms, such as fatigue, pruritus, and anorexia can occur, as well as the classic "B" symptoms (ie, fever, night sweats, and weight loss ≥10% of body weight). Non-Hodgkin lymphoma can be distinguished as lymphoblastic or nonlymphoblastic. The child with lymphoblastic lymphoma often presents with supradiaphragmatic disease and may have cervical or supraclavicular lymphadenopathy, sometimes in association with a mediastinal mass or SVC syndrome (as previously described for T-cell lymphoblastic lymphoma). Central nervous system disease in such children is associated with signs of increased ICP. The patient with nonlymphoblastic lymphoma of the Burkitt or non-Burkitt type often presents with intra-abdominal disease that can manifest as intussusception, abdominal obstruction, hepatosplenomegaly, or obstructive jaundice. The child with sporadic Burkitt lymphoma can present with a rapidly enlarging abdominal mass associated with tumor lysis syndrome. Endemic Burkitt lymphoma (ie, African lymphoma) presents with facial or isolated jaw tumors. Additionally, the patient with lymphoma is at risk for developing 1 or more paraneoplastic syndromes. These include idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, nephrotic syndrome, and peripheral neuropathies, which may be mediated by abnormal and lymphoma-driven humoral or cell-mediated processes. The child with lymphoma is also at risk for tumor lysis syndrome as described for leukemia. Generally, a patient may have entirely normal blood cell counts or a mild anemia, but occasionally the bone marrow may be infiltrated, giving a clinical picture similar to leukemia with anemia, thrombocytopenia, or neutropenia.

Table 152.1. Signs and Symptoms of Childhood Cancer

Disease	*Symptoms*	*Signs*
Leukemia	Fatigue, pallor Bone pain Fever, infection Bruising, bleeding Disseminated intravascular coagulation Superior vena cava syndrome Headache Seizures Oliguria/anuria Abdominal pain, diarrhea	Anemia Neutropenia Thrombocytopenia Lymphadenopathy Hepatosplenomegaly Mediastinal mass Petechiae, purpura Papilledema Cranial neuropathies Renal failure
Brain tumors	Supratentorial tumors Seizures Visual dysfunction Unilateral motor dysfunction Infratentorial tumors Deficits of balance Difficulty breathing Increased intracranial pressure Headache Vomiting Diplopia Motor weakness Loss of developmental milestones	Upper motor neuron signs Marcus Gunn pupils Parinaud syndrome Diabetes insipidus Appendicular dysmetria Sixth nerve palsy Cranial neuropathies Horner syndrome Papilledema Systemic hypertension Setting sun sign Large head size
	Lymphoma	
Non-Hodgkin	Supradiaphragmatic (ie, lymphoblastic) Respiratory difficulty, cough Superior vena cava syndrome Enlarged/enlarging lymph nodes Infradiaphragmatic (small, non-cleaved) Abdominal obstruction Intussusception Abdominal distension	Mediastinal mass ± effusions Lymphadenopathy Abdominal mass Hepatosplenomegaly Obstructive jaundice
Hodgkin	Constitutional symptoms (ie, fever, weight loss, pruritus)	Lymphadenopathy ± matted nodes
Neuroblastoma	Skin nodules Proptosis, raccoon eyes Nystagmus Diarrhea Spinal cord compression symptoms	Hypertension Abdominal mass Hepatosplenomegaly Horner syndrome
Rhabdomyosarcoma	Related to primary site (eg, urinary retention with genitourinary tumors)	Head and neck mass Extremity swelling/mass
Wilms tumor	Rapid development of abdominal swelling Painless hematuria	Abdominal or flank mass Hypertension Associated congenital anomalies Aniridia Hemihypertrophy Urogenital anomalies
Ewing sarcoma	Painful swelling of bone or surrounding soft tissues Constitutional symptoms (ie, fever, fatigue)	Pathologic fracture
Osteosarcoma	Painful swelling of bone	Pathologic fracture

The child with brain tumor can present with diverse signs and symptoms, depending on the anatomic location of the tumor (ie, subtentorial, supratentorial, or brain stem), age of the child (eg, infants with open sutures), and presence and degree of increased ICP. Subtentorial tumors, which are more common in children than adults, typically present with gaze palsies, cerebellar signs (especially truncal ataxia), dysmetria, or vomiting. Supratentorial tumors can cause seizures, upper motor neuron signs (ie, hemiparesis, asymmetrical hyperreflexia, and clonus), sensory changes, behavioral changes, decreased school performance, and disorders of the midbrain (eg, *Parinaud syndrome* [ie, paralysis of upward gaze]). Signs and symptoms of ICP are often in the forefront of complaints. Recurrent morning headaches, headaches that awaken the child at night, intense headaches, vomiting (often followed by temporal relief of morning headaches), lethargy, setting sun sign (ie, eyes deviating downward like a sun setting on the horizon), increasing head circumference and loss of developmental milestones in infants, and change in school performance in older children all warrant close evaluation. Certain conditions, such as tuberous sclerosis and neurofibromatosis 1, should increase the index of suspicion for brain tumor. Primary tumors intrinsic to the brain, that is, those of glial, neural, or choroid plexus origin, and extrinsic to the brain (ie, craniopharyngioma, germ cell tumor) are encountered most often in the pediatric population. Neural/embryonic tumors, such as medulloblastomas and primitive neuroectodermal tumors, are more typical for childhood age group. Metastatic brain lesions are less common in children than adults but may be encountered with neuroblastomas, lymphomas, or some renal tumors.

The child with spinal cord involvement from a primary spinal tumor or a paraspinal tumor (eg, neuroblastoma, Ewing sarcoma, leukemic chloroma) may present with persistent back pain, intense radicular pain, local bony tenderness of the affected vertebrae, abnormal reflexes, abnormal dermatomal sensory examination, weakness/evolving paralysis, and subtle symptoms of bowel or bladder dysfunction (ie, constipation, difficulty urinating). Suspicion of a spinal cord compression is an oncologic emergency for which timely, appropriate consultation must be sought.

Neuroblastoma is a malignancy of sympathetic ganglionic cell origin and can arise anywhere along the sympathetic nervous system. Most tumors arise in the adrenal or paraspinal region of the abdomen; additional sites include the neck, chest, pelvis, and, rarely, CNS. At presentation, tumors may be localized, with or without regional lymph node extension, or disseminated involving bone, bone marrow, liver, and CNS. The child with localized disease often is asymptomatic and the tumor is detected when radiographic imaging is performed for other medical purposes. The child with disseminated disease is ill-appearing and may present with fever, bone pain, and irritability. Paraneoplastic syndromes may also be present at diagnosis, with a variety of features, such as opsomyoclonus/myoclonus/ataxia (ie, random dysconjugate eye movements, myoclonic jerking), cerebellar ataxia, and diarrhea. Proptosis and hemorrhage caused by metastases involving the periorbital region can result in periorbital swelling and ecchymoses (ie, raccoon eyes). A cervical tumor may be associated with unilateral Horner syndrome (ie, unilateral ptosis, miosis, and anhidrosis). Central nervous system metastasis may present with signs and symptoms of increased ICP.

Nephroblastoma or Wilms tumor, an embryonic tumor of the kidney, usually presents as a painless abdominal mass, often detected by a parent while bathing the child. Associated symptoms may include fever, abdominal pain, or hematuria. Abdominal trauma can result in rupture and hemorrhage of these bulky masses, and a child may present with acute abdominal pain and swelling. On examination, the child may have hypertension, stigmata of associated genetic syndromes (eg, Beckwith-Wiedemann, Denys-Drash), or another isolated congenital anomaly, such as aniridia, hemihypertrophy, or hypospadias.

Bone sarcomas that occur in children include Ewing sarcoma, osteosarcoma, and other rarer sarcomas. These tumors are most common in adolescents and rarely occur in young children. Bone tumors can present with pain at the site of tumor, with or without an associated soft tissue mass. Osteosarcomas classically involve the metaphyseal portions of the long bones, with the distal femur and proximal tibia being the most frequently involved sites. Metastatic disease, which is present in 15% to 20% of cases, primarily involves the lung, although other sites of bone can be involved. Ewing sarcomas that occur in bone most commonly involve the flat bones of the axial skeleton. When affecting the long bones, they tend to arise in the diaphyseal region (unlike osteosarcoma). Twenty-five percent of cases will have metastatic disease at presentation involving lung, bone, or bone marrow. The child with Ewing sarcoma may also have associated constitutional symptoms, such as low-grade fever, fatigue, and weight loss. Extraosseous soft tissue components are also more common with Ewing sarcomas than osteosarcomas.

Rhabdomyosarcomas, which account for approximately one-half of the soft tissue sarcomas in children, present with signs and symptoms dependent on the location of the primary tumor. Sites include the head, neck, chest, abdomen, genitourinary tract, or extremities. Less than 25% of children will present with metastatic disease, but when present it can involve lymph nodes, lungs, bone marrow, and bone. Head and neck sarcomas commonly arise in parameningeal and orbital sites and can present with recurrent headache, vomiting, visual problems, and proptosis. Abdominal and pelvic primary tumors can present with a palpable abdominal mass, pain, constipation, urinary obstruction, or dysuria. Genitourinary tract tumors most often involve the bladder or prostate and can present with pain, constipation, and urinary obstruction. One classic presentation occurs in girls who present with a grape-like mass at the introitus and vaginal bleeding; this is caused by tumor involving the vagina or uterus and is known as *sarcoma botryoides*. Primary tumors involving an extremity present with swelling at the site of tumor that can be painful and tender on palpation.

Pathophysiology

Although the macroscopic causes of pediatric cancer are not well elucidated, significant progress has been made in determining some of the cellular and molecular events that actively trigger or fail to prevent malignancy. Growth factors are responsible for stimulation

of cellular proliferation, and growth factor receptors transduce this signal into the cell via cytoplasmic secondary messengers, which in turn transmit the signal to nuclear regulatory factors. These factors ultimately regulate transcription of new RNA and protein, resulting in the desired cellular response of stimulation or inhibition of growth. Malignant cells have a genetic makeup that differs from the constitutional karyotype of the host. A series of mutations occurs in genes that regulate cell growth and differentiation, resulting in dysregulation of cell growth, differentiation, and death. Oncogenes promote cell growth and tumor suppressor genes inhibit cell division. With inappropriate overexpression of an oncogene or underexpression of a tumor-suppressor gene, inappropriate cell growth and division may occur, resulting in a malignant transformation.

Usually, multiple genetic aberrations are present that result in malignant transformation of a cell. One of the most important tumor suppressor genes is *p53*. The *p53* gene encodes for a nuclear protein that is expressed in all cells of the body and serves to induce cell cycle arrest or apoptosis in response to DNA damage. Inactivation of *p53* has been identified in numerous cancers. An initial event can alter or knock out 1 allele of a *p53* gene pair, and a second event results in loss of heterozygosity for that genetic locus. An inherited abnormality of *p53* (ie, Li-Fraumeni syndrome) or a serendipitous accident to *p53* can cause heterozygosity for that gene. If a second event knocks out complete function of *p53*, a DNA-damaged cell can escape the signal to arrest its growth or undergo apoptosis. The result can be a malignant transformation that allows the abnormal cell to grow unchecked. The retinoblastoma gene is another classic and well-studied tumor suppressor, the loss of which results in malignant transformation of the cell.

The threat of cancer to a living organism lies in its uncontrolled growth. By growing unchecked and invading, compressing, and metastasizing to vital organs, malignant cells threaten normal life functions and cause symptoms specific to the affected area of the body.

Differential Diagnosis

Cancer is rare and often challenging to diagnose in children. Many of the presenting symptoms can be nonspecific and easily attributed to more common childhood conditions. To add to the difficulty, a pediatric practice will, on average, see a case every 5 to 7 years. Differential diagnoses for some common childhood symptoms that may suggest an underlying malignancy are discussed herein.

Lymphadenopathy is a common pediatric physical finding and is most frequently the result of infection (see Chapter 100). Acute bacterial adenitis, usually involving the head and neck region, is typically associated with local signs of inflammation, such as erythema, warmth, and tenderness. Cervical adenopathy resulting from viral illness is typically bilateral, and the lymph nodes are usually mobile, soft, and nontender. Generalized lymphadenopathy or regional lymphadenopathy characterized by firm, matted, rubbery lymph nodes should raise the suspicion for an underlying malignancy. Lymphadenopathy that is persistent or progressive, despite empiric antibiotic therapy or resolution of infectious symptoms, also merits further evaluation for malignancy. Leukemia often presents with generalized lymphadenopathy, usually in association with hepatosplenomegaly and abnormal laboratory findings. Lymphoma typically presents with regional lymphadenopathy, often in the cervical or mediastinal region, in conjunction with other signs of systemic illness. Metastatic disease (eg, neuroblastoma, rhabdomyosarcoma) may also present with regional lymphadenopathy. Nonmalignant causes of neck masses that can be mistaken for cervical lymphadenopathy include structural anomalies, such as branchial cleft cysts or cystic hygromas (see Chapter 94).

Bone and joint pain are common symptoms in children with acute leukemia because of bone marrow involvement and may be generalized. This presentation can be confused with various rheumatologic conditions. Localized bone pain is a common presentation for the child with primary bone cancer (eg, osteosarcoma, Ewing sarcoma) and often is attributed by the child or parent/guardian to some trauma. It is not unusual for the diagnosis to be delayed several months. Differential diagnosis includes infection (eg, osteomyelitis), trauma, musculoskeletal conditions, and benign bone lesions.

Headache is a common symptom encountered by the general pediatrician, and few of these headaches are caused by intracranial brain tumors (see Chapter 129). When evaluating a child with headaches, signs to raise the index of suspicion for a brain tumor include persistent vomiting, recurrent morning headaches or headaches that awaken the child, worsening headaches, associated neurologic abnormalities, and visual changes (eg, papilledema on examination). In infants, increasing head size, setting sun sign, and loss of acquired developmental milestones are red flags. The differential diagnosis for headaches in children is broad and includes infections (eg, meningitis, sinusitis), migraines, hydrocephalus, hemorrhage, and seizures.

An abdominal mass in an infant or child is always concerning and merits an evaluation. The most common malignant causes for an abdominal mass in this age range include neuroblastoma, nephroblastoma (ie, Wilms tumor), hepatoblastoma, non-Hodgkin lymphoma (ie, Burkitt lymphoma), sarcomas, and germ cell tumors. Massive hepatosplenomegaly resulting from leukemic or lymphomatous infiltration can also be palpated as an abdominal mass. Nonmalignant etiologies of an abdominal mass may include hepatomegaly or splenomegaly, renal cysts, hemangiomas, or constipation.

Pancytopenia or single cytopenias are always worrisome for a malignancy involving bone marrow. Acute leukemia is the most common malignancy involving bone marrow and can present with leukopenia, anemia, thrombocytopenia, or any combination of these. Any malignancy that can metastasize to the bone marrow (eg, neuroblastoma, lymphoma, Ewing sarcoma, rhabdomyosarcoma) can also produce pancytopenia or depression of 1 of the cell lines resulting from replacement of the bone marrow. Pancytopenia can also occur as a primary bone marrow failure syndrome, such as Fanconi anemia, or as an acquired aplastic anemia resulting from infections (eg, post-hepatitis), drugs (eg, chloramphenicol, anticonvulsant agents), radiation, or idiopathic causes. Transient mild depression

of the cell lines (most often leukopenia or anemia) from infectious causes is quite common during childhood. Depression of more than 1 hematopoietic cell line merits a closer evaluation and consultation with a pediatric hematologist.

Evaluation

History

The history should focus on the duration and evolution of symptoms as well as the presence or absence of constitutional symptoms (eg, anorexia, fever, night sweats, weight loss). The effect of the symptoms on daily activities (eg, school attendance, sports) should be determined and will clue the physician to the scope of the illness. The presence of recent or persistent infections, medications (especially steroids), or unusual environmental exposures should also be ascertained (Box 152.1). Relevant medical history should be considered. A previous cancer diagnosis would raise the index of suspicion for relapse or a secondary malignancy. Certain immunodeficiencies and genetic syndromes are associated with an increased risk for malignancy (eg, trisomy 21 syndrome and leukemia) and should also be considered. A family history of childhood cancers or genetic syndromes is also important.

Physical Examination

A thorough physical examination is essential, with particular attention paid to symptomatic areas (Table 152.1). Generally, the lymph nodes should be carefully assessed for enlargement or malignant characteristics (ie, firm, fixed, rubbery nodes or nodular conglomerates) and the abdomen for organomegaly or masses. The skin should be evaluated for the presence of pallor, petechiae, or purpura that would suggest anemia or thrombocytopenia. A thorough search for signs of persistent infection should be performed and, if present, may reflect bone marrow disease with neutropenia. Neurologic symptoms, including headache, vomiting, or focal concerns, warrant a full neurologic examination. Increased ICP may manifest as papilledema or sixth nerve palsy. In the infant, increased ICP can manifest with a large head size, full fontanels, or setting sun sign. A report of back pain also merits a full neurologic examination with close attention to any sign of spinal cord compression that may be suggestive of a possible spinal or paraspinal mass.

Box 152.1. What to Ask

Cancer

- How long has the child had the symptoms?
- Does the child have a family history of cancer?
- Does the child have a history of constitutional symptoms (eg, fever, weight loss, night sweats)?
- Does the child have a history of recent onset of pallor, fever, bleeding and/or bruising, pain, swelling, hematuria, or malaise?
- Has the child been attending school or participating in routine activities?
- Has the child been exposed to any environmental toxins?
- Has the child been taking antipyretic agents and/or nonsteroidal anti-inflammatory drugs on a regular basis or any prescribed antibiotics or steroids?

Laboratory Tests

In a child with nonspecific or constitutional symptoms concerning for malignancy, it is reasonable to begin with a complete blood cell count, peripheral blood smear, and comprehensive chemistry panel (eg, electrolytes, renal and liver function). If a malignancy is suspected, lactate dehydrogenase is useful as a nonspecific marker for increased cell turnover. If leukemia or lymphoma is suspected, evaluation for tumor lysis syndrome (by checking uric acid, potassium, phosphate, and calcium) should be performed. Additionally, certain tumors secrete or synthesize characteristic markers and metabolites that are pathognomonic for their diagnosis. For example, elevated levels of the sympathetic neurotransmitter metabolites vanillylmandelic acid and homovanillic acid are found in the urine of individuals with neuroblastoma or pheochromocytoma. Tumor markers, such as α-fetoprotein and β-human chorionic gonadotropin, are characteristic of germ cell tumors. Additionally, α-fetoprotein is a useful tumor marker for hepatoblastoma and, rarely, pancreatoblastoma as well. Monitoring of these levels is useful as an indicator of response to therapy or relapse. Other laboratory values, such as ferritin or erythrocyte sedimentation rate, can be elevated and reflect an underlying systemic illness (Table 152.2).

Imaging Studies

Radiologic studies are a necessity in the initial evaluation and staging of most childhood cancers. After the diagnosis of malignancy has been confirmed, appropriate imaging studies to assess the local and metastatic spread of the disease should be performed before the initiation of therapy. The type of studies performed depends on the specific malignancy and its associated pattern of metastatic spread. Common studies performed include plain radiography, computed tomography, magnetic resonance imaging, and gallium or positron emission tomography scans. For leukemias and lymphomas, an initial chest radiograph is necessary to evaluate for a mediastinal mass (most commonly seen in T-cell leukemia/lymphoma). Additional imaging is typically not necessary for leukemia; however, lymphomas warrant further diagnostic imaging for staging, whether computed tomography or gallium or positron emission tomography scans. Required imaging for evaluation of specific childhood cancers is provided in Table 152.2.

Pathology

The child with suspected malignancy should be referred to a children's cancer center where there are specialized pediatric oncologists, radiologists, surgeons, and pathologists who can work together to establish the best approach for diagnosis, whether biopsy or removal of tumor, and handling of tissue. Collection of fresh tissue at biopsy for specialized genetic testing and tumor banking is important and can contribute significantly to a complete pathologic diagnosis.

For certain clinical scenarios, obtaining tissue for pathologic diagnosis is difficult. The child who presents with a large mediastinal mass may be in respiratory distress, for example, secondary to SVC syndrome, and at high risk during anesthesia. In this situation, coordinated

Table 152.2. Diagnostic Tests and Imaging Studies Used in the Evaluation of Common Childhood Cancers

Disease	*Diagnostic Tests*[a]	*Imaging Studies*
Leukemia	Bone marrow aspirate and biopsy Cytogenetic analysis of bone marrow CBC with platelet count, differential, reticulocytes Flow cytometry of peripheral blood PT, PTT, fibrinogen Serum electrolytes, Ca, PO_4 BUN, creatinine, uric acid, LDH CSF cell count, differential, cytology	Chest radiography (look for mediastinal mass) Abdominal ultrasonography for hepatosplenomegaly
Brain tumors	In case of suspected germ cell tumors: serum and CSF α-fetoprotein, β-human chorionic gonadotropin, carcinoembryonic antigen CSF cytology for medulloblastomas, primitive neuroectodermal tumors and ependymomas	MR imaging of brain with gadolinium MR imaging of spine for selected tumors
Lymphoma	CBC with platelet count, differential, reticulocytes Bilateral bone marrow aspirate and biopsy CSF cell count and cytology (EBV PCR for immunocompromised patients with suspected CNS lymphoma) Serum LDH, electrolytes, Ca, PO_4 ESR, ferritin	Gallium scan, PET scan CT of chest, abdomen, pelvis Brain MR imaging for CNS lymphomas
Neuroblastoma	CBC with platelet count, differential Serum electrolytes, liver and renal panel Serum ferritin Serum LDH, uric acid Urine HVA and VMA Bone marrow aspirate and biopsy	CT or MR imaging of primary tumor site CT of chest, abdomen, pelvis (± head) with contrast Bone scan Iobenguane scan
Rhabdomyosarcoma	CBC with platelet count, differential Electrolytes, liver and renal panel Bone marrow aspirate and biopsy CSF cell count and cytology (head and neck primary parameningeal tumors only)	CT or MR imaging of primary tumor site CT of chest, abdomen, pelvis Bone scan, PET scan
Nephroblastoma (ie, Wilms tumor)	CBC with platelet count, differential Electrolytes, liver and renal panel Urinalysis PT, PTT, fibrinogen	Chest radiograph CT of primary tumor site Ultrasonography of inferior vena cava CT of chest Bone scan
Ewing sarcoma	ESR CBC with platelet count Bone marrow aspirate and biopsy Serum LDH	Plain radiographs of primary site CT or MR imaging of primary tumor site CT of chest Bone scan
Osteosarcoma	Bone biopsy	Plain radiographs of primary site CT or MR imaging of primary tumor site CT of chest Bone scan
GCTs (extracranial)	Serum α-fetoprotein β-human chorionic gonadotropin Carcinoembryonic antigen	Chest radiograph (for thoracic lesions) Abdominal (or testicular) ultrasonography CT or MR imaging of primary tumor site CT of chest

Abbreviations: BUN, blood urea nitrogen; Ca, calcium; CBC, complete blood cell count; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; GCT, germ cell tumor; HVA, homovanillic acid; LDH, lactate dehydrogenase; MR, magnetic resonance; PCR, polymerase chain reaction; PET, positron emission tomography; PO_4, phosphate; PT, prothrombin time; PTT, partial thromboplastin time; VMA, vanillylmandelic acid.

[a] Tumor biopsy (with few exceptions, eg, intracranial GCT secreting α-fetoprotein/β-human chorionic gonadotropin, inoperable brain stem gliomas) is required for diagnoses of most malignancies. Rarely, thoracic or abdominal hematologic lymphomas in an unstable patient may be diagnosed from cytology of pleural effusion or ascitic fluids.

efforts should be made to obtain pathology specimens in the least invasive manner, before the initiation of therapy. Diagnosis often can be made by less invasive procedures (eg, complete blood cell count, peripheral blood flow cytometry, bone marrow aspirate/biopsy, thoracentesis) that may require very minimal sedation. If it is necessary to start therapy, biopsy should be performed as soon as clinically tolerated.

Management

If a diagnosis of cancer is suspected or confirmed in a child, referral to a pediatric cancer center where appropriate diagnostic procedures, tissue handling, and treatment can be provided is important.

Diagnosing and managing childhood cancer requires a multidisciplinary team consisting of pediatric oncologists, surgeons, radiation oncologists, pathologists, and other pediatric subspecialists. Additionally, supportive ancillary services, such as social work, child life, child psychology, pain service, palliative care programs, and religious support, are important. When making a referral for a child with a suspected cancer, the referring physician should prepare the family with the physician's suspicions and the likely workup that will ensue at the accepting center. It is also necessary to initiate robust psychosocial support.

Because the management of specific childhood cancers is beyond the scope of this chapter, the discussion herein focuses on the general principles of pediatric oncologic management. The primary therapeutic modalities for the management of childhood cancer include chemotherapy as a systemic treatment, surgery or radiation for local control, and myeloablative therapies followed by hematopoietic stem cell transplantation. Neoadjuvant (preoperative) chemotherapy sometimes is implemented for solid tumors to make surgery feasible with less morbidity and to treat undetectable micrometastases (too small to detect by scanning) upfront. Increasingly, as the molecular aberrations of cancer are becoming understood, cancer-targeted therapies are becoming more prevalent. Conventional, cytotoxic anticancer therapy is likened to a "shotgun" approach in which cancer cells and normal cells are subject to toxicity. The effects of therapy on normal tissues and organs can manifest acutely (limiting the acute dose) or in the long term (affecting quality of life). As more and more children are surviving childhood cancer, the late effects of therapy are increasingly evident, further emphasizing the need for risk-adapted therapy, cancer-targeted therapy, and a reduction of treatment-related toxicities.

The National Cancer Institute Children's Oncology Group initiated a Pediatric MATCH clinical trial using precision medicine to manage advanced solid tumors in children. This trial first screens for genetic changes in tumor samples in search of druggable targets. If such a target is identified, the patient can be enrolled in a corresponding treatment arm to evaluate efficacy of the drug.

Other advances in this field include immunotherapeutic approaches to manage childhood cancer. Promising examples include chimeric antigen receptor T cells and bispecific antibodies that engage immune cells against refractory leukemias, and monoclonal antibodies against neuroblastoma. Other therapies manipulating natural killer cells are in development.

Optimal outcome depends on several factors, including correct pathologic diagnosis; careful medical management, including administration of chemotherapy and monitoring of side effects; precise customization of radiation fields if radiation therapy is necessary; optimal surgical resection for local control, if indicated; and therapeutic ability and experience with administration of treatment to children. Centers that specialize in the management of pediatric cancer are experienced in the diagnosis and treatment of rare malignancies and are thus best equipped to treat affected children. Additionally, the standard of care for children with cancer is treatment according to research study protocols from national collaborative research groups (eg, Children's Oncology Group), available at most specialized pediatric cancer centers. Posttreatment analysis of children treated on protocols at specialized pediatric cancer centers shows disease-free survival rates that are significantly better than those of children treated outside this setting. Similarly, treatment of adolescents and young adults on protocols at specialized pediatric cancer centers yields better outcomes than in those treated by oncologists who typically treat adults. These differences are perhaps the result of greater biological responsiveness of pediatric cancers, better tolerability of multi-agent chemotherapy regimens by younger patients, and, in part, compliance endorsed by parents.

The placement of indwelling central venous catheters is standard in cancer therapy in pediatric patients, making frequent venous access for diagnostic and therapeutic purposes more easily tolerated by children. External catheters (eg, Broviac, Hickman) or internal subcutaneous catheters are selected depending on the underlying diagnosis and intensity of therapy. All indwelling catheters are at risk for infection from contamination of blood (ie, line infections) or infections around the catheter site itself (ie, tunnel infection). Most central line infections can be managed with IV antibiotic therapy; however, certain pathogens (eg, fungi) are difficult to clear and require line removal. Central venous catheters may also be complicated, with thromboses requiring local thrombolytic therapy or long-term (3–6 months' duration) anticoagulation therapy.

In the interest of cost containment and convenience as well as children's well-being, it is often more feasible for children to be closer to home between chemotherapy cycles. The primary care physician should be familiar with the management of various infectious complications to which children undergoing cancer therapy are subject. Fever in the child with neutropenia (especially with absolute neutrophil count ≤500 cells/μL) requires a different therapeutic approach than fever in the otherwise normal child. Until proven otherwise, the child with fever and neutropenia (usually induced by chemotherapy, sometimes in combination with radiation therapy) must be assumed to have a serious bacterial infection. The patient should be treated accordingly, with hospitalization, prompt initiation of IV antibiotics, thorough examination for site of infection, and careful hemodynamic monitoring. Initial treatment consists of wide spectrum antibiotic coverage for *Staphylococcus aureus,* gram-negative enteric organisms, and *Pseudomonas aeruginosa* (eg, cefepime with or without an aminoglycoside, vancomycin). Additional coverage for anaerobic infection (eg, mucositis), viral infection (eg, herpes stomatitis, varicella), and

other pathogens (eg, fungi) depends on the child's treatment history and clinical findings. Additional proactive supportive care, including aggressive antiemetic, anti-constipation, and analgesic regimens; IV hydration; administration of granulocyte colony-stimulating factors; and blood product transfusions, minimizes complications secondary to intensive chemotherapy. Standard of care for a child undergoing chemotherapy also includes *Pneumocystis jiroveci* prophylaxis. Live vaccines are omitted for these children, usually until near complete immune reconstitution takes place after chemotherapy.

Prognosis

The prognosis for children with all forms of cancer has dramatically improved over the past 4 decades. Nearly 80% of children diagnosed with cancer can expect to be long-term survivors. Figure 152.2 shows the improvement in cure rates for the most common childhood cancers. This success is largely the result of the efforts of national collaborative group science and treatment protocols and best can be exemplified by historical improvements of childhood ALL survival resulting from improved therapies (Figure 152.3). With increased survivorship, however, new concerns have arisen with respect to long-term effects of treatment, risks of secondary malignancies, and complex social and psychological issues. In a large study of childhood cancer survivors, adults treated for a childhood cancer in the 1970s and 1980s were 3 times more likely than their siblings to have developed a chronic health condition. Risk-adapted therapies and continued multidisciplinary surveillance of childhood cancer survivors through adulthood will help to optimize more favorable outcomes.

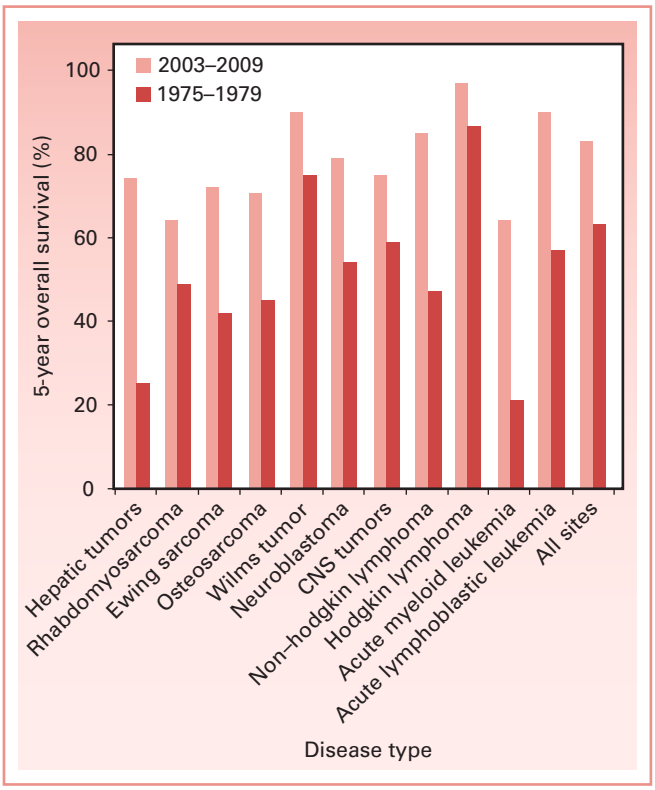

Figure 152.2. Five-year survival rate for 2 time periods for pediatric cancer diagnosed from birth to age 19 years. Five-year survival is presented for all sites (per the International Classification of Childhood Cancer) and specific histologic subtypes contrasting outcomes for children diagnosed between 1975 and 1979 with those diagnosed between 2003 and 2009. Data obtained from the National Cancer Institute SEER program from 9 SEER registries based on patient cases observed through 2010.

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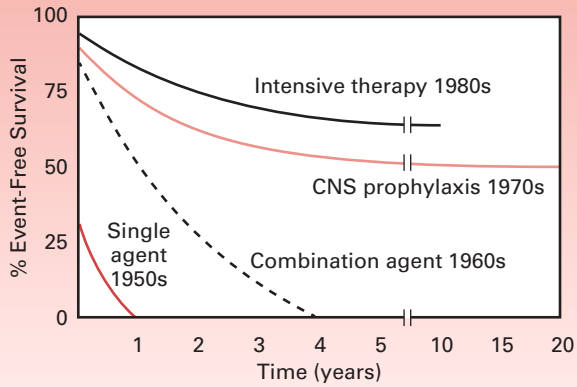

Figure 152.3. Historical perspective of the treatment of childhood acute lymphoblastic leukemia. The single-agent era resulted in few complete remissions and no cures. The combination-agent era without adequate central nervous system (CNS) treatment resulted in high complete remission rates but almost uniform mortality. Between the mid-1960s and the 1970s, combination chemotherapy and CNS treatment resulted in prolonged, disease-free survival for approximately 50% of children. Intensive therapy in the 1980s and 1990s resulted in an event-free survival of 75% to 80% of children.

Reprinted with permission from Silverman LB. Acute lymphoblast leukemia. In Orkin SH, Fisher DE, Look AT, Lux SE, Ginsburg D, Nathan DG, eds. *Oncology of Infancy and Childhood.* Philadelphia, PA: Saunders Elsevier; 2009:297–330.

CASE RESOLUTION

The boy undergoes a mediastinoscopic biopsy of the mediastinal mass, which reveals lymphoblastic lymphoma. No evidence of disease in the bone marrow or spinal fluid is present, which would indicate a worse prognosis. Treatment involves chemotherapy, and the prognosis is quite good. Symptoms of SVC syndrome caused by obstruction from the tumor resolve with shrinkage of the tumor secondary to therapy.

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CHAPTER 153

Chronic Kidney Disease

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CASE STUDY

During a consultation for diarrhea and dehydration in a 7-year-old boy, the pediatrician notes growth retardation. The boy's parents report decreased appetite, decreased level of physical activity, and bed-wetting, despite the patient having been previously potty trained. The medical history is significant for multiple episodes of fever caused by presumed ear infections during his first years after birth and 1 episode of urinary tract infection, without further studies. After hydration, the physical examination reveals a pale and short patient (height 101 cm [39.8 in]; <5th percentile) with a blood pressure of 125/85 mm Hg, the latter of which is indicative of stage 2 hypertension for age, sex, and height. Routine laboratory studies reveal anemia, a serum creatinine level of 1.4 mg/dL, and 3^+ proteinuria.

Questions

1. How is renal function estimated in the pediatric patient?
2. What are the relevant questions to ask about medical and family history in the child who presents with chronic kidney disease?
3. What additional diagnostic tests should be performed to determine the etiology of the kidney disease?
4. What are the approaches to the treatment of the child with chronic kidney disease?

The kidney is mainly responsible for excretion or clearance of waste products; however, it also plays an important role in the regulation of acid-base status, electrolytes, and water and the synthesis of erythropoietin (EPO), renin, and 1,25-dihydroxycholecalciferol. Thus, when the kidney is affected, the regulation of multiple functions is disturbed. To differentiate chronic kidney disease (CKD) from acute kidney injury, CKD is defined as at least 3 months of abnormal renal function. Currently, glomerular filtration rate (GFR) is the best method for the estimation of renal function and for the detection, evaluation, and management of CKD. The GFR varies according to sex, age, and body size and reflects the amount of plasma cleared by the kidney (Box 153.1). It can be challenging to evaluate GFR in children; however, the formula first published in 2009 has been shown to be accurate for a range of GFRs, from 15 to 75 mL/min/1.73 m^2. Early recognition of CKD is important to prevent complications associated with progressive decline in renal function. Signs and symptoms of CKD in children are nonspecific; thus, it is vital that the primary medical professional, usually a pediatrician or family practitioner, recognizes the earliest signs and symptoms of CKD and institutes proper medical care. Prompt referral to a pediatric nephrologist must be made, and follow-up consultations by both physicians should be performed regularly to optimize treatment of these children.

The Kidney Disease: Improving Global Outcomes (KDIGO) "2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease" states that pediatric CKD may be diagnosed by GFR less than 60 mL/min/1.73 m^2 for at least 3 months or GFR greater than 60 mL/min/1.73 m^2 accompanied by evidence of structural abnormalities or other markers of functional kidney abnormalities, including proteinuria, tubular disorders, or pathologic abnormalities detected by histology or inferred from imaging. For children age 2 years or older, kidney function can be staged based on GFR (Table 153.1). Stages 1 and 2 are defined by a GFR of greater than or equal to 90 mL/min/1.73 m^2 and 60 to 89 mL/min/1.73 m^2, respectively. Chronic kidney disease staging is important because management guidelines are based on CKD stage, and CKD progression is associated

Box 153.1. Method of Evaluating the Glomerular Filtration Rate in Children

1. Measuring the true GFR

Reference standard: inulin clearance, iothalamate, iohexol

Expensive, time-consuming

Not for everyday practice

2. Evaluating the GFR

A. Measured from a 24-hour urine collection

$$\text{GFR} = \frac{\text{Urine creatinine (mg/dL)} \times \text{Volume of urine (mL)}}{\text{Time of urine sampling (min)} \times \text{Plasma creatinine (mg/dL)}}$$

GFR (normalized for 1.73 m^2) = creatinine clearance × 1.73/body surface area

B. Estimated from a spot blood sample

GFR (mL/min/1.73 m^2) = 0.413 × Height (cm)/Plasma creatinine (mg/dL)

Abbreviation: GFR, glomerular filtration rate.

with certain comorbidities. Ameliorating CKD-associated comorbidity may reduce long-term cardiovascular disease risk factors and improve clinical outcomes. Particular importance should be placed on managing growth, proteinuria, acidosis, anemia, hypertension, and metabolic bone disease. After the GFR declines to 15 to 29 mL/min/1.73 m^2 (stage 4 CKD), the patient and family should be prepared for renal replacement therapy and possible renal transplantation. End-stage renal disease (ESRD), or stage 5 CKD, is defined as a GFR of less than 15 mL/min/1.73 m^2 or the need for dialysis or transplant. All children with CKD should be referred early to a pediatric nephrologist to facilitate treatment of the patient and education of the family. In adult patients with CKD, late referral is associated with increased rates of morbidity and mortality.

In newborns, normal GFR is less than 60 mL/min/1.73 m^2, and body surface area-adjusted GFR values do not reach adult levels until 2 years of age. Thus, GFR threshold values used to stage CKD are not applicable to children younger than 2 years. Many references exist for normal GFR in preterm and term neonates; among the most comprehensive tables is included in a 2007 review article (see Selected References). Glomerular filtration rate values between 1 and 2 standard deviations below the mean should be considered moderately reduced, and GFR values at least 2 standard deviations below the mean should be considered severely reduced.

Studies of adult patients with CKD have found that morbidity and mortality associates not only with GFR level but also with degree of albuminuria; thus, the 2012 KDIGO guidelines recommend classifying adult CKD by GFR and albuminuria category. Although similar large-scale trials assessing albuminuria severity and clinical outcomes in pediatric patients with CKD are currently lacking, prospective studies are ongoing. As such, albuminuria is not currently used to classify pediatric CKD, although it may be used in future, pending further clinical data accumulation.

Epidemiology

The incidence of CKD in children is unknown. Current estimates are based on the number of children accepted for dialysis and renal transplantation; however, some children do not require dialysis or transplantation until adulthood. In 2008, the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reported 7,037 patients with an estimated GFR of less than or equal to 75 mL/min/1.73 m^2. The causes of CKD can be broadly categorized into 2 main groups: congenital and acquired. Congenital conditions, such as obstructive uropathy, aplasia/hypoplasia/dysplasia, reflux nephropathy, and prune-belly syndrome accounted for most of the diagnoses (53%) reported in 2008 and are referred to by the acronym CAKUT (congenital abnormalities of the kidney and urinary tract). Among the acquired conditions, focal segmental glomerulosclerosis is the most prevalent diagnosis at 9%. Overall, males are more often affected by CKD (64%). Age at registry entry varies, with 20% of children entered into the registry before 2 years of age, 16% between 2 and 5 years of age, 32% between 6 and 12 years of age, 28% between 13 and 17 years of age, and 4% after the age of 17 years; however, time at registry entry does not strictly correspond to age at time of CKD diagnosis.

Clinical and Biologic Presentation

The child with CKD often is asymptomatic or presents with nonspecific symptoms, and abnormal renal function is detected during a routine health examination or screening. For a small percentage of these patients, CKD is incidentally discovered when the patient presents with other illness, such as diarrhea and dehydration. Before receiving a diagnosis of CKD, a patient may also be referred to a specialty physician for the evaluation of growth retardation, hypertension, or anemia (Box 153.2). Occasionally, a history of recurrent episodes of fever without a source or partially treated urinary tract infection (UTI) secondary to undiagnosed vesicoureteral reflux is uncovered. A child may also report vague generalized symptoms, including malaise, anorexia, and vomiting, which may be associated with advanced renal failure.

Metabolic and Water/Electrolyte Abnormalities

The child with a congenital abnormality, such as obstructive uropathy or renal dysplasia, may develop polyuria resulting from an inability to concentrate urine, and salt wasting and polydipsia may become prominent features of the patient's disease. In such cases, blood pressure is usually normal. A history of bed-wetting may therefore be a clue to CKD. In contrast, the child with advanced CKD may have impaired sodium excretion, resulting in water retention and, consequently, fluid overload and secondary hypertension. Hyperkalemia is not an

Table 153.1. Classification of Chronic Kidney Disease

Stage	*Glomerular Filtration Rate (mL/minute/1.73 m^2)*
1	≥90
2	60–89
3a	45–59
3b	30–44
4	15–29
5	<15

Box 153.2. General Symptoms Associated With Chronic Kidney Disease

- Growth retardation/growth failure
- Anorexia
- Anemia
- Bone disease
- Metabolic acidosis
- Hypertension

uncommon component of CKD, and it becomes evident when the GFR falls below 10 mL/min/1.73 m^2. Hypokalemia is a less common problem and may be secondary to excessive diuretic use or strict dietary restriction; it may also be the hallmark of tubulointerstitial disease (eg, proximal tubulopathy) during the early stages of CKD.

Metabolic acidosis is mainly caused by the overall decrease in ammonium excretion from a reduced number of nephrons. Decreased excretion of titratable acid, as well as bicarbonate wasting in cases of proximal renal tubular acidosis, may also play a role.

Glucose intolerance may occur in some children with CKD despite elevated insulin levels. This may occur independently or in association with genetic diseases, such as hepatocyte nuclear factor-1β mutations, which induce renal cysts and atypical diabetes mellitus. The linear correlation between a decline in renal function and insulin resistance even at the early stages of CKD has been shown in adults. More than 50% of children develop hyperlipidemia by the time they reach ESRD. The characteristic plasma lipid abnormality is a moderate hypertriglyceridemia. A high prevalence of hypercholesterolemia and low levels of high-density lipids and albumin are characteristic as well. These derangements have a role in the manifestation of cardiovascular disease.

Growth Failure

Failure to thrive is the hallmark of CKD in children, and the degree of growth retardation varies according to the age of presentation. Because maximal growth occurs during the first few years after birth, children with congenital renal problems are the most affected. In the NAPRTCS, height deficits were greatest for children younger than 5 years, with nearly 50% below the third percentile for age and sex. Growth failure occurs early in the course of CKD and affects up to 35% of this population; by the time of renal transplantation, many children have severe short stature. Moreover, children with more severely impaired renal function tend to have more severe height deficits as well. Sexual development and bone age often are delayed in affected patients. Uremia, anorexia, and frequent vomiting contribute to the protein and calorie malnutrition frequently observed in younger children with CKD. Early, intensive management often is required to maximize nutritional status and optimize growth.

Mineral and Bone Disorders Associated With Chronic Kidney Disease

The effect of CKD on mineral and bone disorders (MBD) may be immediate (eg, biologic disequilibrium of calcium, phosphate, vitamin D, and parathyroid hormone [PTH]) or delayed (eg, growth retardation, bone pain, fractures, bone deformities, extraskeletal and vascular calcifications, increased morbidity and mortality). The development of CKD-MBD begins early in the course of CKD; clinical manifestations include growth retardation and skeletal deformities, such as genu valgum, ulnar deviation of the hands, pes varus, and slipped capital femoral epiphysis. Whereas the term *renal osteodystrophy* refers specifically to different bone lesions as defined by bone histomorphometry, the term *CKD-MBD* is used to define clinical and biochemical abnormalities as well as the long-term consequences of alterations in bone and mineral metabolism associated with CKD. Thus, CKD-MBD is manifested by 1 or a combination of the following abnormalities: abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; abnormalities in bone histology, linear growth, or strength; and vascular or other soft tissue calcification.

Anemia

The anemia of CKD is normochromic and normocytic. Insufficient EPO production occurs in the setting of GFR less than 30 mL/min/1.73 m^2. Anemia is frequently accompanied by decreased serum iron levels, increased total iron-binding capacity, and low reticulocyte counts. The patient undergoing dialysis is predisposed to develop bleeding tendencies secondary to platelet dysfunction and mechanical hemolysis.

Hypertension

The rate of hypertension in children with CKD varies from 38% to 78%. Prolonged hypertension may accelerate deterioration of renal function. An acute rise in blood pressure may cause seizure in a child with CKD. Other manifestations include headache, epistaxis, congestive heart failure, nerve palsies, and cerebral hemorrhage. Hypertension is a frequent finding in children with CKD secondary to polycystic kidney disease or chronic glomerulonephritis.

Cardiac Dysfunction

The patient with CKD is at increased risk for left ventricular hypertrophy (LVH), vascular calcification, and congestive heart failure. Left ventricular hypertrophy, as diagnosed on echocardiography, is present in 75% of adults with CKD; hypertension and anemia are important contributing factors. Left ventricular hypertrophy also occurs in pediatric patients with CKD, with a prevalence of 10% to 20% in CKD stages 3 and 4. Fluid overload, refractory hypertension, severe anemia, and uremic cardiomyopathy may contribute to congestive heart failure.

Neurologic Dysfunction

The child with CKD may have impaired neurodevelopment related to the age of presentation. Memory deficits, lack of concentration, depression, and weakness may occur. Children younger than 5 years are more affected because significant brain growth and maturation occur during the early years. The child with severe uremia may experience global developmental delay and seizures. Unless neurodevelopmental delays are recognized promptly and early intervention is instituted, neurologic dysfunction is often progressive. Some genetic diseases involving cerebral and renal development may play a role in developmental delay.

Pathophysiology

The Final Common Pathways in Nephron Loss

Regardless of the type of initial injury to the kidney, glomerular hyperfiltration and tubulointerstitial damage are the final common pathways of glomerular destruction. Hyperfiltration occurs

as a response by the residual glomeruli to compensate for the loss of nephrons, as summarized in Figure 153.1. Reduced filtration results in increased production of renin and angiotensin-converting enzyme (ACE). The consequent vasoconstriction of the efferent arteriole increases the hydrostatic pressure on the capillary wall, resulting in a compensatory higher filtration rate per nephron but also increased protein transit across the wall. Proteinuria involves recruitment of inflammatory cells and upregulation of proinflammatory and profibrotic genes. Protein overload in tubular cells stimulates their differentiation into myofibroblasts, thus promoting fibrosis. Concurrently, the inflammatory cascade activates the complement system, resulting in additional damage to the kidney. Interstitial fibrosis impairs oxygenation of the tubular cells, and the resulting chronic hypoxia further activates the renin-angiotensin system. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have antihypertensive properties; additionally, they may reduce intraglomerular pressure, proteinuria, and the consequent tubulointerstitial fibrosis, thus potentially slowing the rate of CKD progression.

Growth Failure

Multiple factors are involved in the pathogenesis of growth retardation in children with CKD, including deficient calorie and protein intake, decreased EPO production resulting in anemia, metabolic acidosis, drug toxicity (from corticosteroids) and alterations in the growth hormone (GH)-insulinlike growth factor (IGF)-1 axis. Growth hormone-IGF-1 alterations are characterized by peripheral resistance to GH secondary to decreased expression of GH receptors and decreased levels of the bioactive IGF-1, the primary mediator of somatic growth. This decrease in bioactivity results from the retention of IGF-1 binding proteins (BPs), which worsens as GFR declines. Additionally, renal osteodystrophy in children involves alteration of the growth plate-cartilage architecture, which further contributes to growth failure. Adynamic bone growth (ie, low bone turnover) and severe hyperparathyroidism increase the severity of growth retardation. Also contributing to growth failure is the hypogonadism associated with CKD. In teenagers with CKD, the loss of pulsatile secretion of gonadotropin-releasing hormone contributes to shortening of the pubertal growth spurt and reduced growth velocity.

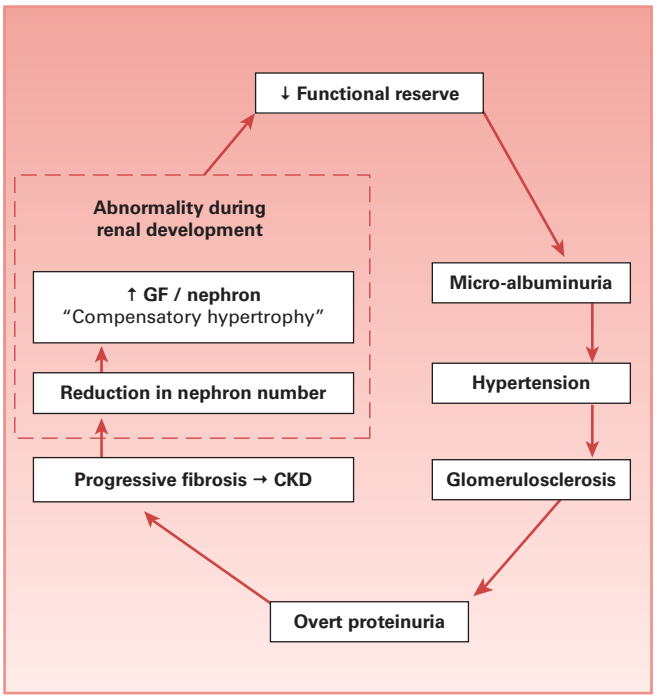

Figure 153.1. The consequences of reduction in nephron number in the pediatric patient.
Abbreviations: CKD, chronic kidney disease; GF, glomerular filtration.

Mineral and Bone Disorders Associated With Chronic Kidney Disease

The development of renal osteodystrophy is multifactorial. Reduced renal mass results in decreased synthesis of 1,25-dihydroxycholecalciferol; in turn, the stimulus to absorb calcium from the gut is decreased. The resultant hypocalcemia and lack of vitamin D feedback on the parathyroid glands stimulate the production of PTH, facilitating rapid mobilization of calcium from the skeleton, thus normalizing serum calcium at the expense of bone. With advancing CKD, skeletal resistance to PTH occurs, and circulating levels of PTH increase.

Hyperparathyroidism and the resultant high bone remodeling produces fibrosis in bone, a condition termed *osteitis fibrosa*. Administration of exogenous vitamin D and its derivatives can suppress such bone remodeling; however, without adequate monitoring, such administration can cause low bone turnover. The physician can monitor for adynamic bone by monitoring serum PTH and alkaline phosphatase levels, which usually are lower in these patients than in patients with secondary hyperparathyroidism and high bone turnover.

Hyperphosphatemia occurs when the few remaining nephrons lose the ability to excrete the daily load of phosphorus from the diet; it is a late phenomenon, usually occurring in CKD stages 4 and 5. Historically, aluminum-containing phosphate binders contributed to the pathogenesis of osteomalacia, a state characterized by poorly mineralized osteoid, and adynamic bone disease; currently, the use of large doses of calcium-based phosphate binders and active vitamin D sterols are implicated in the pathogenesis of osteomalacia. Biochemical abnormalities present in CKD-MBD, including abnormal calcium-phosphate metabolism, hyperparathyroidism, and increased levels of fibroblast growth factor 23 (FGF23), in association with traditional cardiovascular disease risk factors, such as hypertension, hyperlipidemia, hyperhomocysteinemia, anemia, and oxidative stress, contribute significantly to the development of cardiovascular disease, which is the leading cause of death in individuals with ESRD. In young adults with childhood-onset CKD, the prevalence of coronary artery calcification can be as high as 92% when evaluated by sequential computed tomography (CT) with electrocardiogram gating.

In the early 2000s, FGF23 was identified as the pathogenic hormone in various forms of hypophosphatemic rickets and tumor-induced osteomalacia. Secreted by osteocytes, FGF23 functions as a

phosphaturic hormone and as a suppressor of renal 1-α-hydroxylase. Circulating FGF23 levels have been observed to increase early in the course of CKD. Contributing to these elevated levels may be decreased FGF23 clearance, increased synthesis by osteocytes (a compensatory mechanism attempting to maintain normal phosphate levels) or an unintended response to treatment with active vitamin D analogs. In individuals with CKD, elevated FGF23 levels are associated with renal disease progression, cardiovascular morbidity, cardiovascular mortality, and all-cause mortality. In vitro and animal studies have shown that FGF23 may directly induce LVH.

Anemia

Chronic kidney disease anemia begins when the GFR falls below 30 mL/min/1.73 m^2 and is the result of multiple factors, including decreased EPO production, decreased red cell survival, bone marrow inhibition, iron deficiency, vitamin B_{12} and folate deficiency, inflammation, and osteitis fibrosa. Historically, aluminum toxicity was also implicated in CKD anemia. Blood loss during hemodialysis sessions may be contributory, as well. Recently, hepcidin, a hormone synthesized in the liver, was found to be central to the pathogenesis of CKD-associated anemia. Hepcidin causes the internalization of ferroportin, a protein that exports iron from the intracellular space to the extracellular compartment. Decreased hepcidin activity results in iron overload, whereas increased hepcidin activity is associated with anemia. Iron loading and inflammation increase hepcidin levels, and EPO treatment decreases hepcidin levels. As GFR decreases, hepcidin levels increase, resulting in ferroportin internalization, intracellular iron sequestration, and functional iron deficiency, thereby contributing to the anemia of CKD.

Differential Diagnosis

Initially, the main challenge for the physician is not determining a differential diagnosis but instead determining whether renal impairment is acute or chronic and, if chronic, the etiology. A variety of kidney problems, whether congenital, hereditary, acquired, or metabolic, may result in CKD. Although specific cures are not available for most of these renal conditions, a complete diagnostic workup is essential to determine the etiology of the renal disease. Such information may identify the presence of an inherited problem that may require genetic counseling and, in some cases, may aid in anticipating problems associated with renal transplantation. Some renal diseases, such as focal segmental glomerulosclerosis and atypical hemolytic uremic syndrome, may recur after renal transplantation, and the patient and family must be informed early about this possibility in preparation for renal transplantation. The different etiologies of CKD, as well as their prevalence in the 2008 NAPRTCS registry, are summarized in Table 153.2.

Table 153.2. Etiologies of Pediatric Chronic Kidney Disease According to the 2008 North American Pediatric Renal Trials and Collaborative Studies

Condition or Disease	*Disease*	*Percentage*[a]
CAKUT	Obstructive uropathy	20.7
	Aplasia/hypoplasia/dysplasia	17.3
	Reflux nephropathy	8.4
	Prune-belly syndrome	2.7
Genetic diseases	Polycystic disease	4.0
	Cystinosis	1.5
	Oxalosis	0.1
	Denys-Drash syndrome	0.1
	Congenital nephrotic syndrome	1.1
	Medullary cystic disease	1.3
Glomerular diseases	Focal segmental glomerulosclerosis	8.7
	Chronic GN	1.2
	MPGN type I	1.1
	MPGN type II	0.4
	Immunoglobulin A nephritis	0.9
	Henoch-Schönlein nephritis	0.6
	Idiopathic crescentic GN	0.7
	Membranous nephropathy	0.5
Systemic diseases	Hemolytic uremic syndrome	2.0
	Systemic lupus erythematosus	1.6
	Wegener granulomatosis	0.4
	Other systemic immunologic diseases	0.4
	Diabetic nephropathy	0.2
	Sickle cell nephropathy	0.2
Miscellaneous	Familial nephritis	1.6
	Pyelonephritis/interstitial nephritis	1.4
	Renal infarct	2.2
	Wilms tumor	0.5
	Other	15.8
	Unknown	2.6

Abbreviations: CAKUT, congenital abnormalities of kidney and urinary tract; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis.

[a] Total exceeds 100 because of rounding.

At initial presentation, it is necessary to distinguish acute from chronic renal failure because therapeutic strategies may differ and long-term renal prognoses can be quite different as well. Hereditary diseases commonly encountered include hereditary nephritis (eg, Alport syndrome), branchio-oto-renal syndrome, and juvenile nephronophthisis. Acquired diseases, such as chronic glomerulonephritis, membranoproliferative glomerulonephritis, and focal and segmental glomerulosclerosis, affect a large percentage of older children who progress to CKD. Whereas anemia, hypertension, and fluid and electrolyte abnormalities often are associated with both chronic *and* acute renal failure, suboptimal linear growth and signs

and symptoms of renal osteodystrophy manifest over time and occur in patients with chronic renal impairment.

Evaluation

A complete evaluation of the child presenting with renal failure must be performed, including careful history and physical examination, along with laboratory tests and appropriate imaging studies.

History

A thorough history must be obtained, including a complete and detailed family history, because this may aid in diagnosis (Box 153.3). A prenatal history, including possible drug exposures and results of antenatal imaging, may also provide useful information.

Physical Examination

A complete physical examination is required. Height and weight must be measured accurately, and the results should be plotted on the same growth curves used for healthy children. Weight may be overestimated if fluid retention is present. Blood pressure must be taken, using an appropriately sized cuff. Blood pressure measurements should be compared to the 50th percentile for age, sex, and height. The presence of tachycardia, heart murmurs, or adventitious heart sounds that may be indicative either of uncompensated anemia or of cardiac or pericardial involvement must be noted. Gross eye examination should be performed, including fundal examination, to assess for evidence of chronic hypertension. Macular abnormalities or hearing problems may be indicative of a heritable disease, such as Alport syndrome. Ear abnormalities (eg, preauricular pits, ear tags) accompanied by hearing deficits may be associated with renal disease (eg, branchio-oto-renal syndrome). Undescended testes may be evident in some children with urogenital problems.

Box 153.3. What to Ask

Chronic Kidney Disease

Child

- Were any abnormalities, such as hydronephrosis or polyhydramnios/oligohydramnios, noted on prenatal ultrasonography?
- Does the child have a history of prolonged illness, pallor, weakness, vomiting, or loss of appetite?
- Does the child have any history of headaches or visual or hearing problems?
- Does the child have any history of hematuria, proteinuria (evidenced by foamy or bubbling urine), urinary tract infections, or episodes of fever with unknown source?
- Does the child have impaired growth or development compared with siblings and other children?
- Does the child have any problems with micturition, such as dribbling or weak stream on urination?
- Does the child have increased passage of urine (ie, polyuria) or chronic excessive thirst and fluid intake (ie, polydipsia)?
- Does the child have daytime or nighttime urinary incontinence (ie, enuresis)?
- For any question to which the parent or guardian answered "yes," what was the age at presentation?

Family

- Does any family member have kidney disease, including hematuria, proteinuria, kidney cysts, or urinary tract infections, or has any family member undergone any urologic surgery?
- Does any family member have need of dialysis or kidney transplantation?
- Does any family member have a history of ear/hearing problems or eye abnormalities?

Laboratory Tests

For the initial laboratory workup, complete blood cell count, electrolyte levels, blood urea nitrogen level, creatinine level, calcium level, phosphorus level, and urinalysis should be obtained (Figure 153.2). Glomerulonephritis usually presents with numerous red blood cells, white blood cells, proteinuria, and a variety of casts in the urine. In the patient with proteinuria from whom a 24-hour collection is impossible, quantified excretion should be estimated by a protein-creatinine ratio in a spot urine sample. A ratio greater than 0.2 is abnormal and is well correlated with urinary protein excretion greater than 4 mg/m^2 per hour in a 24-hour urine collection. In nephrotic syndrome, the proteinuria is usually greater than 40 mg/m^2 per hour. Immunologic studies, including complement C3, complement C4, antinuclear antibody, and anti–double-stranded DNA, as well as a minimal infectious disease evaluation for hepatitis B and C, should be obtained if the renal disease is suggestive of an immune complex-mediated glomerulonephritis, such as systemic lupus erythematosus, postinfectious glomerulonephritis, or membranoproliferative glomerulonephritis.

Imaging Studies

Ultrasonography is by far 1 of the best imaging tools in the assessment of patients with CKD. Renal ultrasonography yields important information, such as kidney size, echogenicity, and the presence of hydronephrosis, cysts, or stones, that may help establish the diagnosis of the renal disease. The presence of small kidneys usually is indicative of chronic disease that may date to fetal development. Increased echogenicity with normal kidney size usually is indicative of medical renal disease.

Voiding cystourethrography is indicated in the patient with hydronephrosis and recurrent UTI to diagnose vesicoureteral reflux and evaluate the anatomy of the upper urinary tract. The use of spiral CT in the evaluation of patients with renal failure has increased in the past few years. This procedure requires relatively less time than standard CT and can be used to evaluate the kidney parenchyma as well as the upper and lower urinary tract.

Nuclear imaging of the kidneys has provided vital information in the workup of children with CKD. Generally, nuclear studies are not routinely done unless specifically indicated. A technetium Tc 99m mertiatide scan may be used to assess renal plasma flow. Technetium Tc 99m dimercaptosuccinic acid scanning may be used to assess

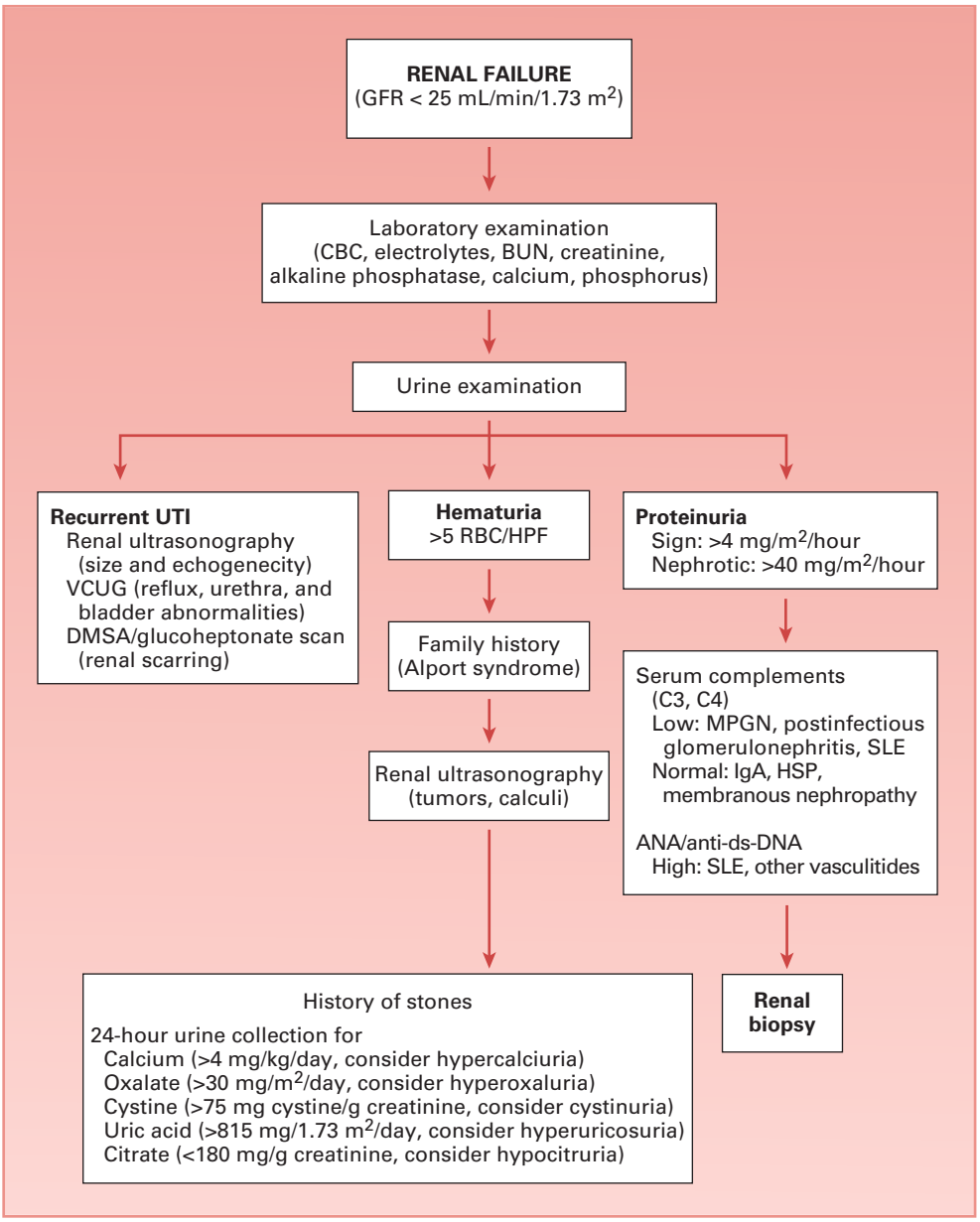

Figure 153.2. Initial diagnostic workup of a pediatric patient with chronic renal failure.

Abbreviations: ANA, antinuclear antibodies; BUN, blood urea nitrogen; CBC, complete blood cell count; DMSA, dimercaptosuccinic acid; ds, double-stranded; GFR, glomerular filtration rate; HPF, high-power field; HSP, Henoch-Schönlein purpura; IgA, immunoglobulin A; MPGN, membranoproliferative glomerulonephritis; RBC, red blood cell; SLE, systemic lupus erythematosus; UTI, urinary tract infection; VCUG, voiding cystourethrography.

renal parenchymal involvement in the patient with acute pyelonephritis and/or recurrent UTIs. This nuclear imaging study provides excellent images of the renal parenchyma and often is used to detect renal scarring in the patient with recurrent UTI. Significant renal parenchymal scarring portends the development of hypertension later in life.

Management

The treatment of children with CKD has markedly improved over the last 2 decades and is summarized in Figure 153.3. Newer treatment options and earlier intervention strategies have greatly improved the lives of affected children. Care of these patients must be managed by multidisciplinary teams involving the primary care physician, nephrologists, nurses, social workers, nutritionists, and psychologists. Comprehensive management includes treatment of the primary disease and comorbid conditions, growth optimization, slowing disease progression, preserving residual renal function, preventing CKD-MBD and cardiovascular disease, and preparing for renal replacement therapy and renal transplantation as CKD progresses. To delay the progression toward ESRD and cardiovascular mortality, medical management of the patient with CKD includes strict control of hypertension; prevention of obesity; control of

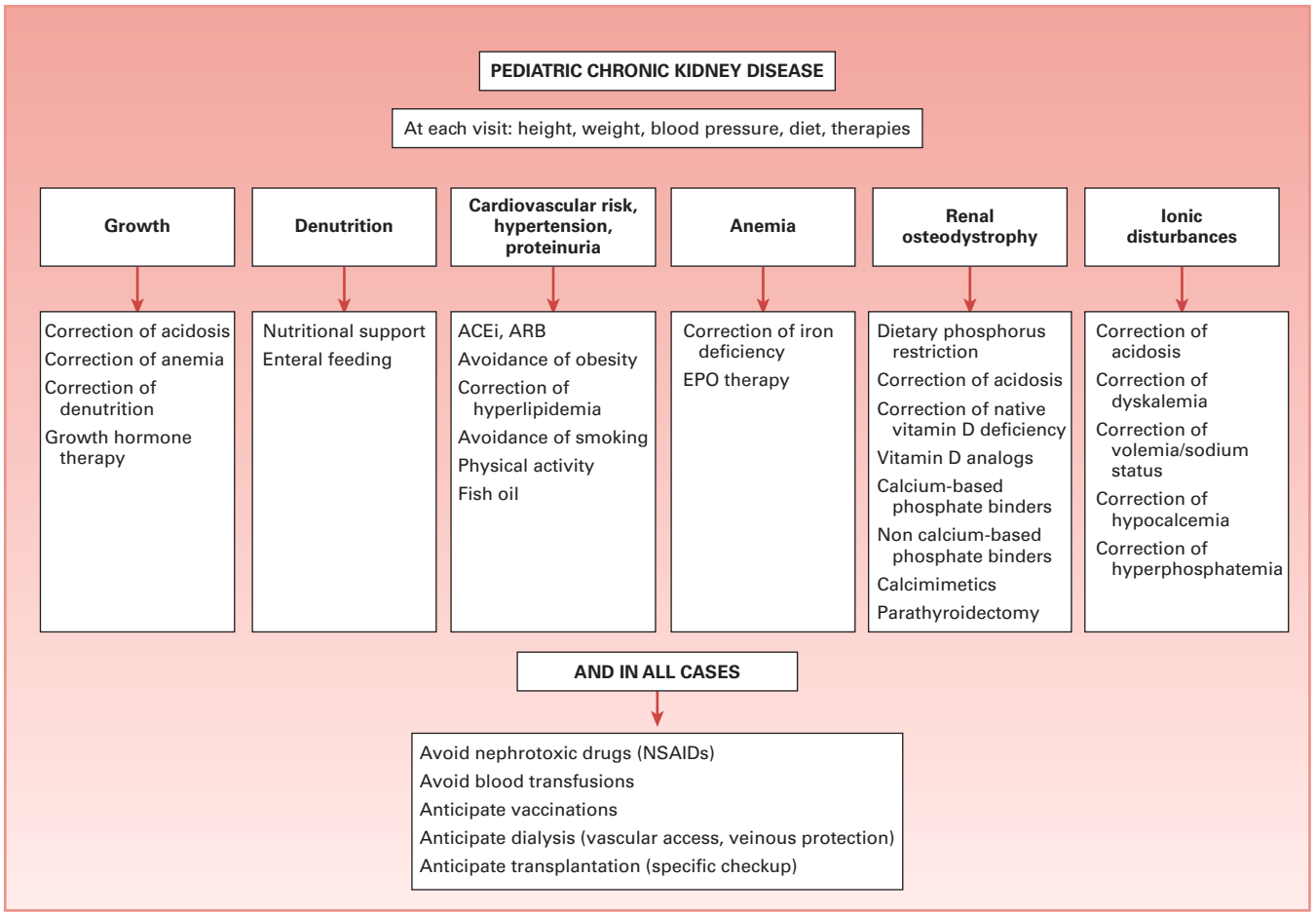

Figure 153.3. Overall management of pediatric chronic kidney disease.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; EPO, erythropoietin; NSAIDs, nonsteroidal anti-inflammatory drugs.

proteinuria with ACE inhibitors or angiotensin receptor blockers; management of serum calcium, phosphorus, and PTH levels; anemia management; and prompt treatment of infections.

Malnutrition: Metabolic and Water/Electrolyte Abnormalities

Dietary management remains an important and challenging aspect of the overall management of the child with CKD. Frequently, these children are anorectic and require supplementation with fat, carbohydrates, and protein. Some patients, especially younger children, may require enteral feeding by nasogastric or gastrostomy tube to meet their daily nutritional requirements. The child with CKD should receive the recommended daily allowance for protein and calories according to age and sex, with adjustment made depending on weight gain. Protein restriction is not advised; studies have shown that restriction of protein intake does not delay the progression of renal failure in these patients. Close monitoring of nutritional status should be performed at each visit, with serial measurements of height and body weight; in children younger than 3 years, head circumference should also be measured.

Daily salt and fluid intake among patients may vary. The patient with hypertension may require relative dietary salt restriction. Conversely, the patient with congenitally obstructed, dysplastic kidneys or nephronophthisis often exhibits polyuria and salt wasting, requiring increased fluid intake and sodium supplementation.

Oral base therapy should be used to maintain bicarbonate levels above 22 mEq/L, as recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines, because metabolic acidosis may have many deleterious effects, including worsening of bone disease, growth retardation, increased muscle wasting, decreased albumin synthesis, resistance to insulin, stimulation of inflammation, and increased overall mortality.

Most children with CKD do not develop hyperkalemia unless their renal function falls below 10 mL/min/1.73 m^2. Initially, dietary intervention may be sufficient, but this is difficult in infants and small children whose diet is limited to formula and only a few solid foods. Pharmacologic interventions, such as loop diuretic agents and polystyrene sulfonate, are used to manage hyperkalemia in these children. In situations of an acute rise in the serum potassium level, emergent measures must be implemented (Box 153.4). Sodium bicarbonate, insulin/glucose, and β_2 agonists (eg, albuterol) acutely decrease the serum potassium level by facilitating intracellular potassium uptake. If the hyperkalemia is unresponsive to conservative medical measures, dialysis must be performed immediately. In the setting of fluid overload and hyperkalemia, diuretic use may be indicated; potassium-sparing diuretics, such as spironolactone,

Box 153.4. Management of Hyperkalemia

- Calcium gluconate, 0.5 mL/kg of 10% solution, or calcium chloride, 0.2 mL/kg of 10% solution (IV).
- Sodium bicarbonate, 2 mEq/kg per dose (IV).
- Glucose-insulin solution, 0.5 g/kg glucose with 0.25 U of insulin per gram of glucose (IV; monitor serum glucose closely).
- Diuretic agent (loop type; potassium-sparing diuretic agents should not be used): furosemide, 1 mg/kg per dose (IV).
- Polystyrene sulfonate (eg, Kayexalate), 1 g/kg per dose orally (if awake) or rectally. (Do not use in patients with any gastrointestinal problems or anomalies.)
- Dialysis (if hyperkalemia persists despite previously noted measures).

Abbreviation: IV, intravenous.

should not be used. Additionally, in patients with impaired concentrating and diluting mechanisms, diuretic therapy should be avoided, because some of these children may have polyuria and become dehydrated on diuretic therapy.

Of increasing concern is the management of lipid disturbances in CKD because of the role of lipids in the progression of renal disease. The routine use of lipid-lowering agents in children with hypercholesterolemia and hypertriglyceridemia remains controversial because of reported liver and muscle toxicity associated with some of these medications. Further studies are warranted to test the efficacy and safety of these medications in the pediatric population.

Growth Failure

Use of recombinant human growth hormone (rhGH) therapy has improved the management of growth retardation in children with CKD; it should be considered in children with height below the fifth percentile. The 2012 KDIGO international guidelines recommend that children and adolescents with CKD stages 2 through 5 with related height deficits should be treated with rhGH when further growth is desired, after first addressing malnutrition and the biochemical abnormalities of CKD-MBD. In several studies, rhGH has been found to have a positive effect on linear growth, although results vary according to CKD stage at the initiation of rhGH. In the NAPRTCS database, catch-up growth after rhGH therapy was observed in 27% of children with chronic renal insufficiency, 25% of children who underwent renal transplantation, and only 11% of children undergoing renal replacement therapy. These findings highlight the need for early management of growth failure in pediatric patients with CKD. Moreover, the response during the first year of treatment correlates with final height. Growth hormone administration is continued until the patient reaches the 50th percentile for mid-parental height or renal transplant is achieved. Growth hormone therapy is contraindicated in the patient with a history of malignancy, hyperglycemia, hyperinsulinemia, or significant scoliosis.

A recent retrospective multicenter US study noted the underprescription of rhGH therapy in pediatric patients with CKD and reported that greater than 50% of short children with CKD did not receive rhGH. The most common reasons were family refusal, severe secondary hyperparathyroidism, and noncompliance; however, in up to 25% of cases, no evident rationale was determined. Waiting for insurance company approval resulted in a significant delay in the initiation of rhGH therapy in 18% of patients. Access to rhGH therapy should be a high priority. Newer treatment modalities targeting GH resistance (eg, recombinant IGF-1, recombinant IGFBP-3, IGFBP displacers) are under investigation for the management of growth retardation in pediatric patients with CKD.

Mineral and Bone Disorders Associated With Chronic Kidney Disease

For the management of renal osteodystrophy, dietary phosphorus restriction is reinforced in children with CKD; however, adherence to this dietary modification is generally poor secondary to unpalatability of the food. Additionally, many processed foods contain large amounts of phosphorus that are overlooked by caregivers despite appropriate nutritional counseling. These foods contribute considerably to phosphorus intake.

When dietary phosphorus restriction proves insufficient to maintain normal phosphate levels, phosphate-binding medications are necessary. Calcium-based binders are most commonly used; however, large doses of calcium-based binders have been associated with an increased risk of vascular calcifications. Thus, non-calcium-based binders, such as sevelamer carbonate and sevelamer hydrochloride, are being used more frequently. Currently, aluminum-containing phosphate binders are infrequently used because of the risk of aluminum toxicity and should be avoided as first-line therapies. If used, precautions must be taken in children who are concomitantly treated with citrate-containing medications, because citrate enhances aluminum absorption, thus enhancing toxicity risk.

Secondary hyperparathyroidism often manifests in children with CKD. The 2012 KDIGO guidelines recommend a serum PTH level within the normal range in patients with CKD stages 1 and 2, and a serum PTH level between 2 and 9 times the upper limit of normal in patients undergoing dialysis. Between 15 and 60 mL/min/1.73 m^2, the optimal level of PTH is unknown; however, a persistently elevated and/or progressively rising PTH level requires attention to modifiable factors, such as hyperphosphatemia, hypocalcemia, high dietary phosphate intake, and vitamin D deficiency, as the first step in management. Because of a lack of association with clinically relevant outcomes and a risk of hypercalcemia, the use of activated vitamin D sterols in the patient with predialysis CKD is recommended only as a means of maintaining age-corrected serum calcium levels. In the patient with CKD stage 5 on dialysis with sufficient vitamin D as well as normal calcium and phosphorus levels but with elevated PTH levels, treatment with activated vitamin D sterols (eg, calcitriol, doxercalciferol) may be warranted. The patient receiving activated vitamin D sterols should be frequently monitored for the development of hypercalcemia or hyperphosphatemia; in such cases, dose modification or phosphate binder adjustment may be necessary. Although calcimimetic agents (eg, cinacalcet) have been shown to be effective in reducing PTH and FGF23 levels in adults, the effects of these agents on the growing skeleton have not yet been well studied in pediatric patients. Thus, the child receiving cinacalcet should

be closely monitored, specifically for hypocalcemia, with appropriate dosage adjustments made as necessary.

If present, 25-hydroxyvitamin D deficiency may require treatment. Optimal levels of 25-hydroxyvitamin D are greater than 30 ng/mL (75 nmol/L). Vitamin D deficiency is highly prevalent in pediatric patients across the spectrum of CKD (40%–80%), resulting from several factors, such as low dietary intake, chronic illness, skin changes, and sometimes urinary losses in patients with proteinuria.

Anemia

The use of recombinant human EPO in the anemia associated with CKD has become a standard of treatment. The correction of anemia results in improved appetite, increased physical activity, and more important, avoidance of the risks associated with blood transfusion. Before the availability of EPO, most patients received frequent blood transfusions, increasing their risks of infection, transfusion reaction, and development of antibodies. The goal is to maintain hemoglobin between 11 and 12 g/dL. Iron stores are assessed by transferrin saturation and ferritin levels and should be maintained between 20% and 50% and between 200 and 800 ng/mL, respectively. The elucidation of the hepcidin pathway and an improved understanding of the pathophysiology of anemia has led to the development of new therapeutic modalities in adults, including prolyl hydroxylase inhibitors, EPO-receptor agonists (eg, Peginesatide), oxygen-carrier products, and *GATA* inhibitors. Trials using these agents in pediatric CKD-associated anemia have shown promising results.

Arterial Hypertension

For chronic management of hypertension in the pediatric patient with CKD, antihypertensive medications should be started if blood pressure measurements are consistently above the 90th percentile for age, sex, and height. The 2012 KDIGO CKD guidelines suggest that the blood pressure goal should be less than or equal to the 50th percentile for age, sex, and height unless achievement of this target blood pressure is limited by signs or symptoms of hypotension. Updates to pediatric hypertension thresholds and management are provided by the 2017 American Academy of Pediatrics "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents." Drugs currently used to manage hypertension in children with CKD include ACE inhibitors, diuretic agents, adrenergic blockers, peripheral vasodilators, and calcium channel blockers. Angiotensin-converting enzyme inhibitors are often used as first-line antihypertensive agents in children with CKD and, as mentioned previously, treatment with ACE inhibitors has been shown to be beneficial in reducing proteinuria, which may help inhibit proteinuria-associated tubulointerstitial inflammation and fibrosis. Angiotensin-converting enzyme inhibitors must be used with caution in patients with a solitary kidney and those with renal artery stenosis, because these medications may acutely decrease kidney function and precipitate hyperkalemia in patients with renal failure. Sexually active adolescent females must be informed about the adverse effects of ACE inhibitors in pregnancy, including renal tubular dysgenesis in the fetus. Calcium channel blockers, especially nifedipine, have been used in cases of severe hypertension because of their rapid onset of action. For patients with poor adherence to daily oral medications, clonidine is currently available in the form of transdermal patches. However, patients should be warned of central nervous system side effects, as well as rebound hypertension if the patch is removed abruptly. If hypertension is secondary to fluid overload and salt retention, aggressive fluid removal with diuretic therapy should be initiated. The patient with long-standing hypertension must regularly undergo echocardiography to assess for LVH and serial ophthalmologic examinations to assess for pathologic changes of the eye. The 2017 American Academy of Pediatrics pediatric hypertension guidelines also recommends strong consideration of routine ambulatory blood pressure monitoring in children with CKD to evaluate hypertension severity and abnormal circadian variations. For uncontrollable hypertension, which often occurs secondary to fluid overload, dialysis may be indicated (Box 153.5).

General Measures

In all cases, anticipation of dialysis or transplantation should begin early in the course of CKD, because many patients with CKD may progress to ESRD and require renal replacement therapy. Protection of upper extremity veins, in anticipation of the need for possible future vascular access, is important. Additionally, blood transfusions should be avoided to the extent possible to prevent the development of hyperimmunization, thereby potentially compromising a future transplant.

Children with CKD, as well as their siblings and household contacts, should receive all standard vaccines, including varicella, influenza, and *Streptococcus pneumoniae*. The patient on immunosuppressive treatment because of glomerulonephritis or after transplant should not receive live-virus vaccines. Every attempt to administer live-virus vaccines, such as measles, mumps, rubella, and varicella, should be done before transplantation. Because children with CKD have a decreased ability to mount an immunologic response, repeated vaccination to induce protective serum antibody titers may be necessary.

Box 153.5. Indications for Initiation of Dialysis

- Severe fluid overload
  - — Congestive heart failure
  - — Uncontrollable hypertension
- Uremic neuropathy
  - — Paresthesia
- Electrolyte abnormalities unresponsive to medical management
  - — Intractable metabolic acidosis
  - — Hyperkalemia
- Pericarditis
- Severe renal osteodystrophy
  - — Extraskeletal calcification
  - — Severe skeletal deformities
- Progressive malnutrition and severe growth retardation, especially in the first year after birth
- Severe anemia or bleeding diathesis

A review of all medications should be performed at every visit to adjust dosages according to kidney function, detect possible adverse effects, and identify any potentially dangerous drug interactions. Monitoring drug levels may be desirable when using antibiotics, anticonvulsant agents, digoxin, theophylline, and anticoagulant agents. To prevent toxicity, dosages of all medications should be altered based on estimated GFR. Special care should be taken when using antibiotics (eg, aminoglycosides, vancomycin) as well as nonsteroidal anti-inflammatory drugs, because of possible detrimental effects on residual kidney function, even in the early stages of CKD.

For contrast-requiring imaging studies in patients with GFR less than 60 mL/min/1.73 m^2 undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media, the 2012 KDIGO CKD guidelines recommend avoidance of high osmolar agents; use of the lowest possible radiocontrast dose; withdrawal of potentially nephrotoxic agents before and after the procedure; adequate hydration with saline before, during, and after the procedure; and measurement of GFR 48 to 96 hours after the procedure.

As stated in the 2012 KDIGO CKD guidelines, indications for referral to a pediatric nephrologist include acute or chronic reduction in renal function, poorly treated or severe hypertension, severe electrolyte abnormalities, the finding of significant abnormalities in urinary tract structure, the presence of systemic diseases likely to produce renal effects, the need for education in progressive conditions, performance and interpretation of renal biopsies, and allaying parental/guardian or patient anxiety. Early referral may provide the opportunity to slow renal disease progression and may result in improved clinical outcomes.

Timing of Dialysis Initiation

For the pediatric nephrologist, the conversation with the patient's family about renal replacement therapy is initiated early in the CKD course. Timing of dialysis initiation is determined not by a certain GFR threshold but rather by multiple factors, including patient signs and symptoms, laboratory values, possibility of transplantation, and family circumstance. Generally agreed-on absolute indications for dialysis initiation include neurologic consequences attributable to uremia, hypertension unresponsive to antihypertensive therapy, pulmonary edema unresponsive to diuretic agents, pericarditis, bleeding tendency, and refractory nausea or vomiting. Relative indications may include less severe symptoms of uremia, hyperkalemia, hyperphosphatemia, malnutrition, and growth failure. Such indications for dialysis often occur when the GFR declines to less than 15 mL/min/1.73 m^2; however, some patients may remain asymptomatic despite a GFR below the aforementioned value, and other patients may warrant consideration for dialysis at higher GFRs.

Prognosis

The prognosis for children with CKD has changed in the last 2 decades. Options for dialysis (ie, hemodialysis, peritoneal dialysis) and kidney transplantation (ie, deceased donor, living-related donor) should be discussed before the occurrence of ESRD. Strategies such as preemptive transplantation (ie, transplantation before the need for dialysis) are likely preferred by the patient and family but may not be achievable because of the median time on the waiting list. Technical advances in dialysis allow the pediatric nephrologist to offer dialysis options to a child of any age and have made long-term survival possible while children await renal transplantation.

Kidney transplantation is the ultimate treatment for the child with CKD. Improvements in immunosuppressive medications and availability of other therapeutic strategies have considerably increased patient and graft survival after kidney transplantation. Full recovery and return to normal activities should be achieved after these children have undergone successful renal transplantation.

CASE RESOLUTION

The patient has a GFR of 30 mL/min/1.73 m^2. The initial evaluation reveals anemia (hematocrit 28% [normal: 36–48]), low serum bicarbonate (17 mEq/L [normal: 22–26]), hypocalcemia (8 mg/dL [normal: 8.6–10]), hyperphosphatemia (7 mg/dL [normal: 2.7–4.5]), and elevated PTH (700 pg/mL [normal: 10–65]). Ultrasonography reveals that both kidneys are small with increased echogenicity, and voiding cystourethrography reveals bilateral vesicoureteral reflux. Management of the primary disease is started with antibiotic prophylaxis to prevent further UTIs, and the patient is referred to pediatric urology. Measures to slow the progression to ESRD are initiated, involving dietary intervention and management of comorbid conditions. Bicarbonate is started for metabolic acidosis; iron and recombinant human EPO are started for anemia; and calcium carbonate is started as a phosphate binder/calcium supplement. The hypertension associated with proteinuria is best managed with an ACE inhibitor. Growth hormone will be considered after the acidosis, anemia, and hyperparathyroidism are corrected. Immunizations are current. An appointment with the pediatric nephrology team is scheduled.

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CHAPTER 154

Diabetes Mellitus

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CASE STUDY

A 10-year-old girl presents with a 3-week history of nocturnal polyuria. Her mother reports that her daughter, previously overweight, seems to have lost weight in the past 2 months after receiving nutrition education. Laboratory tests reveal that the girl's serum sodium level is 130 mEq/L; potassium, 3.2 mEq/L; glucose, 324 mg/dL; and 1+ ketones. Urinalysis reveals specific gravity of 1.025 and moderate glucose and ketones. Her height and weight are within normal ranges for her age, and the remainder of her physical examination is unremarkable.

Questions

1. What is the pathophysiology of type 1 and type 2 diabetes?
2. What are diagnostic criteria for differentiating type 1 and type 2 diabetes?
3. What are the objectives of therapeutic interventions in the child with diabetes?
4. What diagnostic evaluations are used in ongoing management of diabetes?
5. What are the acute and chronic complications associated with diabetes?
6. What is the role of "tight glycemic control" in children and adolescents?

Diabetes mellitus is the second most common chronic illness after asthma among children in developed countries. Diabetes mellitus is a metabolic imbalance that results from insulin deficiency, impairment of insulin action, or both. Advancement in the knowledge of the pathophysiology supports the assessment that diabetes is a heterogeneous disease involving immunologic, environmental, and genetic factors. This has led to a categorization of diabetes based on its pathophysiology rather than the therapeutic intervention. Diabetes associated with absolute insulin deficiency and impaired beta cell function is called type 1 (DM1) (previously juvenile onset or insulin-dependent), and diabetes associated with insulin resistance as well as impaired beta cell function is called type 2 (DM2) (previously adult onset or non-insulin-dependent).

Epidemiology

Overall, diabetes affects 9.4% of the population in the United States. The prevalence among adults age 18 years and older is 12.4%, while the prevalence among children and adolescents younger than 20 years is 0.23%. Diabetes mellitus type 1 and DM2 have been increasing in incidence among youth. From 2002–2003 to 2012–2013, DM1 increased from an incidence of 19.5 cases in 100,000 youths per year to an incidence of 21.7 in 100,000 youths per year. In the same time frame, DM2 increased from an incidence of 9.0 cases in 100,000 youths per year to 12.5 in 100,000 youths per year. Additionally, the populations affected by DM1 and DM2 seem to differ. Type 1 diabetes mellitus is seen equally among girls and boys, with the highest incidence among white youth. Type 2 diabetes mellitus is more prevalent among girls and has the highest incidence among black, Mexican American, and Native American populations. The peak age of presentation for DM1 is between 5 and 15 years. Less is known about DM2 in children, but previous studies show a mean age of 13.8 years at presentation.

The SEARCH for Diabetes in Youth Study is a population-based, observational study of physician-diagnosed diabetes among youth younger than 20 years from centers based in 5 states—South Carolina, Ohio, Colorado, California, and Washington. Much of the current epidemiologic data concerning DM1 and DM2 among youth in the United States has been determined from the data collected in this study.

Monogenic forms of diabetes are uncommon, comprising approximately 1% of all diabetes cases, which include neonatal diabetes (onset in the first 6 months after birth), and maturity-onset diabetes of the young.

Clinical Presentation

Children can vary in their clinical presentation from being asymptomatic to having fulminant metabolic imbalance (Box 154.1). Type 1 diabetes mellitus commonly presents with a classic triad of polydipsia, polyuria, and polyphagia. The most consistent presenting concern is increased urinary frequency, manifested as nighttime polyuria or secondary enuresis. Alterations in appetite and thirst are most commonly recognized when disease onset occurs in the preschool years, likely because parents and guardians are most able to monitor eating and drinking behaviors during the child's first few years. Weight loss can be variable but is more common in DM1 than in DM2. Recent trends indicate that diabetic ketoacidosis (DKA) occurs at the time of initial presentation in up to 31.1% in DM1 and

Box 154.1. Diagnosis of Diabetes Mellitus

- Symptoms (ie, polydipsia, polyuria, polyphagia) together with a random plasma glucose ≥200 mg/dL
- Fasting blood glucose ≥126 mg/dL (confirmed on a subsequent day)
- Oral glucose tolerance test with 2-hour peak plasma glucose ≥200 mg/dL
- Hemoglobin A_{1C} ≥6.5%

5.7% in DM2. Diabetic ketoacidosis presents with vomiting, polyuria, dehydration, and Kussmaul respirations. Children and adolescents with DM2 also report having the classic triad of symptoms but often are identified through screening urinalysis. Type 2 diabetes mellitus is strongly associated with obesity (body mass index ≥95th percentile [see Chapter 155]), acanthosis nigricans, and having a first-degree relative with DM2.

Pathophysiology

The patient with DM1 has an absolute insulin deficiency resulting from autoimmune destruction of the beta cells of the pancreas. The disease process is thought to be triggered by an environmental factor, such as a virus or toxin, in the genetically susceptible individual. Exposure occurs in early childhood, but disease progression can be variable. More than 90% of affected individuals carry human leukocyte antigen-DR3 or -DR4. Discordance of disease among twins supports the theory that DM1 involves an environmental exposure in genetically susceptible individuals. Twin studies show evidence of a preclinical autoimmune process, which also has predictive value in identifying susceptible individuals at risk for developing DM1. Immune changes include an increase in activated T-cells expressing human leukocyte antigen–DR, islet cell antibodies (ICA), insulin autoantibodies, glutamic acid decarboxylase (GAD) antibodies, and islet antigen 2 (Table 154.1).

Table 154.1. Predictive Tests for Individuals Susceptible to Type 1 Diabetes Mellitus[a]

Immunologic Marker(s)	*Risk of Developing DM1 (Within 5–8 years)*
ICA	25%–70%
Anti-GAD antibodies	68% among siblings of DM1 proband and 50% in the general population
IA-2 antibodies	58% among siblings of DM1 proband and 43% in the general population
IAA	Variable (may not be specific to islet cell tissue)
Reduced first-phase insulin release	100%
Anti-ICA and IAA	90%
Human leukocyte antigen with index case	25%–30%

Abbreviations: DM1, type 1 diabetes mellitus; GAD, glutamic acid decarboxylase; IA-2, islet antigen 2; IAA, insulin autoantibodies; ICA, islet cell antibodies.

[a] Individuals with first-degree relative with type 1 diabetes.

Disordered immune function, in which some antigenic components of pancreatic islet cells are not recognized as self, seems to be the pathogenic mechanism for the development of DM1. It is generally believed that at least 90% of beta cell mass must be destroyed before problems with glycemic regulation are manifest. Endogenous insulin deficiency, occurring as a natural consequence of islet cell destruction, results in the inappropriate use of carbohydrate. Cellular uptake of glucose by liver, muscle, and adipose tissue is blocked. Synthesis of glycogen, protein, and fat is reduced, and a catabolic state marked by lipolysis, proteolysis, and ketone body formation ensues. Increased serum glucose and ketones present an overwhelming osmotic load to the kidneys, resulting in urinary losses of volume and cations (Na^+, K^+, NH_4).

The autoimmune phenomena described previously are not evident in DM2 as demonstrated by the absence of ICAs, insulin autoantibodies, and GAD antibodies. This disease, which is characterized by resistance to insulin, may assume different presentations in childhood. The more traditional form of DM2 presents in older children and adolescents and is strongly associated with obesity and having a first-degree relative with DM2. Like adults with DM2, insulin resistance is present, but the existence of a relative insulin deficiency is necessary to develop DM2.

Differential Diagnosis

Diagnosis is usually straightforward given the symptomatology, except in children who present at a very young age. Although the onset of diabetes is rare before 1 year of age, the disease may present with nonspecific symptoms (ie, irritability, vomiting, tachypnea, poor weight gain). When diabetes presents before 1 year of age, or in a child with a strong family history of diabetes and no evidence of autoantibodies or insulin resistance, monogenic causes of diabetes warrant consideration. Chemotherapeutic agents (eg, L-asparaginase) and a variety of medications (eg, corticosteroids, diuretics, oral contraceptives, phenytoin, epinephrine) may induce glucose intolerance. Immunosuppressants taken by transplant recipients also cause hyperglycemia. Glycosuria without evidence of ketosis or elevated blood glucose occurs in certain renal conditions (eg, Fanconi syndrome, carbohydrate malabsorption syndromes, heavy metal intoxication). Transient hyperglycemia, with or without glycosuria, may occur in response to physiological stress (eg, burns, trauma, hyperosmolar dehydration). In most of these cases, glucose regulation returns to normal within several days.

Evaluation

Evaluation should focus on the diagnosis of diabetes (ie, hyperglycemia) and the category because DM1 and DM2 can have different treatment modalities and disease courses.

History

The history should focus on classic symptomatology and whether a family history of diabetes exists. Up to 80% of youth with DM2 will report a positive family history of diabetes, compared with 20% of

youth with DM1. Additionally, exogenous causes of diabetes should be ruled out. Obtaining a history of viral infections or chemical exposures during early childhood may be useful (Box 154.2).

Physical Examination

Growth parameters should be measured and plotted on standard growth curves. Obesity is present in 96% of youth with DM2, compared with 24% of youth with DM1. Although DM1 usually is associated with weight loss as part of the presenting symptomatology, even those patients with obesity and with DM2 may have lost weight prior to presentation. Youth with uncomplicated DM1 may have an unrevealing physical examination, whereas those with DM2 may have physical findings associated with obesity. One study demonstrated that 60% of adolescents with DM2 had acanthosis nigricans and 32% had hypertension at presentation. An intercurrent infection may trigger the symptomatology and should always be sought in cases of ketoacidosis. The child who presents with ketoacidosis may have evidence of vomiting, dehydration, Kussmaul respirations, or in severe cases, altered mental status.

Laboratory Tests

Initial laboratory tests should include evaluation of the serum and urine for glucose and ketones. For the patient presenting with DKA, evaluation should also include a full chemistry panel to assess for metabolic acidosis, hypokalemia, and serum osmolality. After the diagnosis of diabetes is suspected, further testing can assist in categorizing the type of diabetes. Tests include anti-GAD and anti-ICAs, the presence of which support the diagnosis of DM1 (Table 154.1) and insulin and C peptide levels, the latter of which is a marker of insulin levels. Insulin and C peptide levels are usually higher in patients with DM2 because they have insulin resistance rather than an absolute insulin deficiency. Insulin reserve can be measured by determining the basal and stimulated levels of C peptide (≥0.6 ng/mL basal level, ≥1.5 ng/mL 90 minutes after nutritional supplement such as Sustacal or Ensure High Protein). In categorizing diabetes, it is important to note that some individuals with DM1 can have insulin reserves up to 2 years after diagnosis.

Oral glucose tolerance tests may be necessary to confirm the diagnosis of diabetes in cases in which the onset of symptoms is not obvious. Two-hour postprandial values greater than or equal to 200 mg/dL or fasting glucose of 126 mg/dL or higher are evidence of diabetes. The introduction of the intravenous glucose tolerance test with measurement of first-phase insulin release has allowed early diagnosis of individuals at risk for the disease prior to development of symptoms.

Recently, the American Diabetes Association (ADA) added hemoglobin A_{1c} (HbA_{1c}) of 6.5% or greater as an additional criterion that may be used to diagnose diabetes. If such a value is found in a patient, a second test should be performed to confirm the result, and evaluation should proceed to assess for the presence or absence of ketones and type of diabetes.

To assess children who are at risk for DM2, screening may be done every 2 years starting at age 10 years or at the onset of puberty (whichever comes first) using fasting plasma glucose (as recommended by the ADA), oral glucose tolerance test (as recommended by the World Health Organization), or HbA_{1c} (as recommended by the ADA). Children who should be screened are those who meet criteria for obesity and have 2 or more of the following risk factors: family history of DM2 in first- or second-degree relatives, at-risk race/ethnicity (black, Asian/Pacific Islander, Native American, Hispanic), or associated signs and symptoms of insulin resistance (eg, acanthosis nigricans, dyslipidemia, hypertension, polycystic ovary syndrome).

Box 154.2. What to Ask

Type 1 Diabetes Mellitus

- Is the child having increased urination (eg, nighttime urination, unusual bed-wetting)?
- Is the child drinking or eating more than usual?
- Has the child experienced any weight loss?
- Has the child been taking or had access to any kind of medications (eg, corticosteroids, L-asparaginase, diuretic agents ["water pills"], birth control pills)?
- Are there any family members with diabetes (first- or second-degree relatives)?

Management

Early diagnosis together with a comprehensive program of education and aggressive management are essential to prevent acute and long-term complications. Long-term objectives of therapeutic intervention in the child with diabetes are to facilitate normal physical growth and psychological and sexual maturation, promote euglycemia through regulation of glucose metabolism, prevent acute complications (ie, hypoglycemia, ketoacidosis), prevent or delay long-term sequelae, and accommodate physiological changes that alter therapeutic needs (eg, exercise, adolescence, intercurrent illness).

Effective management requires a multidisciplinary team of professionals skilled in handling the myriad issues that arise for families and children with diabetes. Most clinics specializing in the care of children with diabetes include a nurse educator, dietitian, social worker, psychologist or behavioral health specialist, and pediatric endocrinologist. In settings in which such special care centers are available, the primary care physician serves as a key adjunct, underscoring the importance of ongoing patient-family involvement in disease management and ensuring optimal growth, development, and nutrition. In the absence of a special care center, the primary care physician assumes responsibility for all aspects of management, including management of acute complications, monitoring adherence and treatment effect, and surveillance for long-term complications.

Effective therapeutic intervention is based on individual needs for energy, insulin, and exercise. Several factors, including physical growth, insulin requirement, glycemic control, and activity level, influence those needs and must be assessed on a regular basis. For

DM1, insulin therapy is the mainstay of management, whereas DM2 therapeutic options include weight control through diet and exercise (see Chapter 155), oral hypoglycemic agents, and insulin. Oral hypoglycemic agents can decrease blood glucose by increasing insulin secretion, increasing insulin sensitivity, decreasing hepatic glucose output, or decreasing nutrient absorption. These agents include sulfonylureas and other insulin secretagogues, metformin hydrochloride, thiazolidinediones, and acarbose. Although DM2 may initially be managed with exogenous insulin, metformin is the oral agent prescribed most often for DM2 in children and adolescents because it has been approved by the US Food and Drug Administration for pediatric use. A newer class of medication acts by an incretin effect and increases glucose-dependent insulin secretion. This class includes exenatide (administered by injection). A complementary drug inhibits dipeptidyl-peptidase-4 (DPP-4), which cleaves the incretin. Therefore, the DPP-4 inhibitor prolongs the incretin effect to promote endogenous insulin release after a meal. Yet another new class of medications includes sodium-glucose cotransporter-2 inhibitors, which inhibit the reabsorption of glucose in the kidney. Similar to most drugs for the treatment of DM2, these newer drugs do not have a pediatric indication.

Insulin

The purpose of insulin therapy is to enable the affected child to approach euglycemia in response to adequate amounts of food, insulin, and exercise. The amount of daily insulin required is dependent on the child's age, weight, and development. On average for DM1, the child younger than 5 years requires 0.6 to 0.8 U/kg, the child between 5 and 11 years of age requires 0.75 to 0.9 U/kg, and the child or adolescent between 12 and 18 years of age requires 0.8 to 1.5 U/kg in a 24-hour period. Within 3 to 4 months of diagnosis, most individuals experience a partial remission, or honeymoon phase, during which time their insulin requirements decline dramatically. Conversely, illness, anxiety, and adolescence (ie, pubertal changes) may cause the insulin requirement to increase. Even under conditions of increased need, reported daily insulin dosages in excess of 2 U/kg of body weight should stimulate investigations into patient adherence.

Several insulin regimens currently in use take advantage of the variable onset of action of different insulin preparations (Table 154.2). The new insulin analogs are monomers of insulin rather than insulin aggregates. They provide a rapid onset and a shorter duration of action. This allows for easier adjustment of insulin dose depending on the child's appetite because the injection can be given immediately before the meal. The child with newly diagnosed diabetes should use a semisynthetic or recombinant human insulin preparation to minimize the possibility of allergic reaction. Any change in insulin preparation should be undertaken cautiously and only under medical supervision because brands vary in strength, purity, and glycemic response.

Morning hyperglycemia may result from 1 of 2 phenomena, which must be distinguished because the appropriate therapeutic responses are opposite. The *dawn phenomenon* likely involves a nocturnal surge of growth hormone, resulting in hyperglycemia that is present during the night (2:00–4:00 am) and is sustained until morning. Treatment involves increasing the evening dose of intermediate-acting insulin or moving the evening insulin to bedtime. In the *Somogyi effect*, morning glucose is high as a physiological response to nighttime hypoglycemia. Management of this condition requires decreasing the evening intermediate-acting insulin or increasing the carbohydrate content of a bedtime snack.

Adolescents require special consideration. The sexual maturation process occurs in the setting of relative insulin resistance, other hormonal alterations, and a burden of developmental tasks, which make glycemic control problematic at best. Daily insulin requirements may increase to 1.5 to 2 U/kg during adolescence but return to prepubertal levels at the end of the teenage years. Particular efforts must be made to ensure physical and psychological growth in the context of these special tasks. Dietary manipulation and consideration of alternative (usually more intensive) insulin and monitoring regimens is critical for successful glycemic control during this challenging period.

Continuous subcutaneous insulin infusion pumps afford the advantages of programmed variable basal rates and insulin dosing during specific times of the day. In a long-term study on outcomes among children with DM1, children on pumps had fewer hypoglycemic events and hospitalizations for DKA and improved HbA_{1c}. Although insulin pumps are not widely used in young children because of the potential risk of mechanical malfunction and catheter problems (resulting in hypoglycemia or hyperglycemia), they may be considered in children with unstable diabetes or to provide very low doses of insulin. Recent technologic advances have led to development of a hybrid closed loop system, which combines insulin pump and continuous glucose monitoring technology to allow continuous, automatic adjustment of insulin infusion based on the patient's blood glucose patterns.

Table 154.2. Commonly Used Insulin Preparations[a]

Type	*Onset of Action*	*Duration of Effect*
Rapid-acting analogs Lispro, aspart, glulisine	Within 15 minutes	≤5 hours
Short-acting Regular	Within 30 minutes	5–8 hours
Intermediate-acting[b] (zinc or protamine) Neutral protamine Hagedorn	1.5–2.5 hours	18–24 hours
Long-acting[b] Glargine Detemir Degludec	 70 minutes 1.5–2.5 hours 1 hour	 22–24 hours 20–24 hours ≥24 hours

[a] Twice-daily injections: Two-thirds of the total daily dose before breakfast made up of intermediate- and short-acting insulin in 2:1 ratio. One-third before dinner made up of intermediate- and short-acting insulin in 1:1 ratio.

[b] Bedtime dose: Intermediate- or long-acting insulin with regular insulin or short-acting insulin analog before each meal.

Glucose Monitoring

Self-monitoring of glycemic response through the in-home assessment of blood glucose levels is critical to effective therapy. The introduction of reflectance meters (ie, glucometers) has obviated the need for inaccurate, visually read strips of glucose-sensitive paper. The patient who is taking insulin should measure glucose 4 to 7 times daily. Most endocrinologists advocate testing before each meal and at bedtime during the first year after diagnosis. Testing may also be done at 2:00 am to test for hypoglycemia or hyperglycemia. Depending on the age of the child, an acceptable range for glycemic control is 80 to 150 mg/dL. Additional short-acting insulin may be given to correct for high blood glucose. Patients also need to monitor their urine for ketones whenever their blood glucose readings exceed 240 mg/dL.

Glycosylated HbA_{1c} measurements reflect glucose control over the preceding 2 to 3 months. The normal value is 4% to 5.6% of total hemoglobin, and the target value for individuals with diabetes is less than or equal to 7.5%. Glycosylated hemoglobin values less than 7% are excellent, between 7% and 8% are good, between 8% and 10% suggest need for improvement, and more than 10% are poor. The Diabetes Control and Complications Trial studied the effect of different levels of glycemic control on the complications of diabetes. Although the study only included pediatric patients 13 years or older, the study did show that patients with "tight glycemic control" had lower HbA_{1c} levels and fewer long-term complications than patients not tightly controlled. Adolescents with tight glycemic control had a greater risk of hypoglycemic events than the control group, a fact that must be taken into consideration in determining ideal glycemic control for a child. Generally, tight glycemic control is not recommended for children younger than 5 years; for older children, glycemic control should be individualized to the patient. Whenever a child's routines undergo dramatic change, stepped-up home monitoring and medical consultation are advisable. Caution should be used in interpreting HbA_{1c} values in infants and others in whom fetal hemoglobin or other hemoglobin variants are present because these hemoglobin variants may falsely elevate or lower the value of HbA_{1c}. Although compliance with intensive regimens is an indisputable challenge (particularly as responsibility for management shifts from parent or guardian to child), increasing evidence underscores the importance of tight glycemic control.

Since the turn of the 21st century, continuous glucose monitoring systems have become increasingly available to patients as a part of routine diabetes care. Continuous glucose monitoring involves placement of a sensor subcutaneously to measure blood glucose in the interstitial fluid. The advantages of this system includes production of more blood glucose monitoring data without adding to the burden of fingerstick blood glucose. Continuous glucose monitoring may be a highly effective tool alone or with an insulin pump device, to observe trends of low or high blood glucose, allowing the patient and health professional to adjust insulin dosing accordingly to prevent hypoglycemia and to decrease blood glucose excursions.

Nutrition

The timing, amount, and types of foods eaten for meals and snacks should be relatively consistent from 1 day to the next to match the relative constancy of the exogenous insulin. Standard daily caloric requirements are distributed in the following fashion: carbohydrate, 50% to 55% (≤10% in the form of sucrose); protein, 20% to 25%; and fat, 25% to 30% (6%–8% polyunsaturated, ≤7%–10% saturated). In DM2 with overweight/obesity, however, the patient may benefit from overall reduced calorie intake (carbohydrates ≥130 g/day). The distribution of calories should be approximately 25% for breakfast, 25% for lunch, 30% for dinner, and 20% for snacks. Snacks are an important part of the nutrition regimen for the child with diabetes. Most nutritionists recommend 3 snacks for young children (between meals and at bedtime) and 2 for older children. Dietary discipline is a tremendous challenge for many children. Introducing 1 change at a time may make such dietary manipulations more acceptable over the long term. Additionally, establishing healthy eating habits requires availability of healthy choices in the child's environment. Cooperation from the school and home enhances the likelihood of a child developing healthy eating practices.

Carbohydrate counting is an important part of matching insulin requirements to nutritional intake. For the patient on multiple daily insulin injection schedules, flexibility exists in tailoring each dose of insulin based on the carbohydrate content of each meal or snack. For the patient on a twice-daily insulin injection regimen, consistent carbohydrate content of meals and snacks is important in maintaining blood glucose levels. Learning carbohydrate counting takes time for patients and families, and ongoing nutrition support must be provided to help them become familiar and comfortable with how different foods affect patients' blood glucose levels.

Exercise

Exercise contributes to glucose control by facilitating the use of glucose without the assistance of insulin. If not carefully undertaken on a regular basis, exercise can precipitate acute hypoglycemia. Physical activity enhances the body's sensitivity to insulin and can even decrease the daily insulin requirement. Thoughtful planning of exercise involves compensatory changes in food intake and insulin doses. For example, extra energy intake at bedtime may offset the nighttime hypoglycemia that accompanies late afternoon exercise. Seasonal physical activities may necessitate an adjustment in the insulin regimen at certain times of the year.

Education

The role of education is pivotal to the successful management of diabetes in childhood and throughout life. During childhood, educational efforts must be focused on the entire family unit. The affected child must be involved as early as possible and in ways that are developmentally appropriate. The process should involve the early introduction of basic survival information, such as insulin therapy and management of complications. This can be followed by more detailed information, including strategies to reduce long-term sequelae.

Prognosis

Diabetic ketoacidosis is the major cause of morbidity and mortality in children and adolescents, followed by hypoglycemia. Clinical signs of hypoglycemia in older children include shakiness, blurred vision, and dysarthria. Concerns about the neurodevelopmental effect of hypoglycemia in young children have led to the recommendation of more liberal glycemic control in early onset disease. Diabetic ketoacidosis, precipitated by an intercurrent infection or poor compliance, is a metabolic derangement that always requires urgent medical attention and often necessitates hospitalization. Replacement of fluids, attention to electrolyte abnormalities, and insulin therapy are the mainstays of treatment in the face of this complication.

An increase in the number of pediatric patients presenting with hyperglycemic hyperosmolar state (HHS) has occurred. Because management of HHS differs from that of DKA, it is necessary for the physician to be aware of HHS. In fact, treatment for children with HHS may be different from treatment of this disorder in adults.

Long-term complications include proliferative retinopathy, nephropathy, peripheral and autonomic neurologic impairment, and early onset of cardiovascular disease. Ophthalmologic evaluation, overnight urine protein measurement, and a detailed neurologic examination should occur once or twice a year depending on the duration of disease. Intensive therapeutic intervention results in significant reduction in retinopathy, nephropathy, and cardiac and peripheral vascular disease. Preliminary evidence warrants consideration of such therapy with the expectation of benefit in long-term outcomes.

CASE RESOLUTION

With the presence of ketones, the girl is admitted to the hospital to initiate insulin treatment and determine appropriate dosing. Anti-GAD and anti-ICA levels are ordered to determine if she has autoimmunity, which would indicate DM1. She and her family require ongoing education. Careful management is necessary to optimize normal growth and development as well as to delay or prevent long-term sequelae.

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CHAPTER 155

Childhood Obesity

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CASE STUDY

A 10-year-old girl is brought to the office by her mother to discuss concerns about the child's weight, which is 59 kg (130 lb). Her height is 140 cm (55 in), giving her a body mass index of 30 (>95th percentile for age). The remainder of the physical examination, including vital signs, is normal. The mother, who also has overweight, says she does not want her daughter to "end up like me." The patient says she gets teased at school about her weight. The history reveals that this patient is an only child who lives with her single mother in low-income housing in a large city. The mother works the day shift as a nurse's aide at a nearby nursing home. Because the mother is often tired, meals are simple and frequently consist of prepackaged foods, such as pastries for breakfast and frozen dinners for supper. At school, the girl buys her lunch, which usually includes whole milk, a processed entrée, and a dessert. After school, the girl goes home, where she watches television and snacks on chips and soda until her mother arrives home from work. The mother does not allow her daughter to play outside because the neighborhood is unsafe.

Questions

1. How is obesity defined and measured, and what are some pitfalls in measurement?
2. How do genetic susceptibility and environment interact to influence an individual's risk for obesity?
3. What are the complications of childhood obesity?
4. What is the role of the primary care physician in addressing childhood obesity?
5. How can obesity be managed in a supportive, nonstigmatizing way?

Childhood obesity is of significant concern because children with overweight are more likely to have overweight as adults and are at increased risk for multiple chronic conditions. Additionally, having obesity carries a psychosocial toll for affected adults and children, because it remains among the most stigmatized conditions. Children with obesity are often shunned by peers at school, feel isolated, and have fewer friends, whereas adolescents with obesity complete less schooling, go on to have lower household incomes, and are more likely to live in poverty than their counterparts without obesity. The primary care physician is usually the first (and often only) resource available to help patients and their families in screening, diagnosing, discussing, and managing childhood obesity.

Defining obesity presents certain challenges. Ideally, a measure of obesity would correlate with adiposity and predict morbidity and mortality. Body mass index (BMI) (weight in kilograms divided by height in meters squared) is the best and most widely used surrogate measure for obesity but does not completely correlate with adiposity for all individuals. Standards for adults have established a BMI of 25 or greater as overweight and 30 or greater as obese, based on increased risk of morbidity and mortality above these levels. Although BMI currently is the preferred method for assessing degree of obesity in children, other criteria are also used (Box 155.1). Experts classify children at the 85th to 95th percentile of BMI for age as having overweight and those greater than the 95th percentile of BMI for age as having obesity. Because BMI is not a direct measure of adiposity, it is important to recognize that not all children who meet the BMI criteria for overweight and obesity will have adverse health effects of their weight status. A helpful general rule is that the higher the BMI rises above the 95th percentile, the greater likelihood of adverse health effects. For BMI greater than the 99th percentile, which is associated with the most comorbidities, often a switch is made to using a BMI number, as for adults, or alternatively, the percentage above the 95th percentile. The BMI changes as children age because of changes in their proportion of bone mass and lean-to-fat tissue composition. After approximately 1 year of age, BMI-for-age values begin to decline and continue to do so during the preschool years until the BMI reaches a minimum at approximately 5 to 6 years of age, before rising throughout the remainder of childhood, into adolescence and adulthood. This phenomenon of increasing BMI after the nadir in the preschool years is referred to as *adiposity rebound*. Early adiposity rebound (age <4.8 years) is a predictor of later obesity and can be used clinically to identify children at risk.

Box 155.1. Diagnosis of Obesity

- Body mass index >95th percentile for age and sex (≥85th percentile is overweight)
- Body mass index >99th percentile or 120% above the 95th percentile is considered severe obesity
- Weight-for-height >95th percentile (typically used for children younger than 2 years)
- Greater than 120% of ideal body weight for height and age

Epidemiology

The prevalence of obesity is on the rise globally, especially in developed countries. Between 1980 and 2000, the percentage of overweight children and adolescents in the United States tripled, reaching 17.1% in 2003 to 2004. Since then, no significant increases have been seen overall among the US youth population, except for increases in the highest BMI group (>97th percentile). Severe obesity affects 4.5 million U.S. children and adolescents. Hispanic, black, and Native American individuals are disproportionately affected. People with lower education and those in poverty are at highest risk. Prevention and treatment of obesity is important to avoid health risks that affect the individual and are costly to society as a whole. In the United States, the overall spending associated with overweight and obesity was $93 billion in 2002 dollars, one-half of which was publicly financed through Medicare or Medicaid.

Clinical Presentation

The child with obesity usually presents to the physician in 1 of 2 ways. The parent(s)/guardian(s) or the child may come in concerned that the child has overweight (as in the case study). The physician must then consider the growth parameters and BMI for age to make an appropriate determination of the child's overweight status. The more common presentation is the parent who does not recognize that the child has overweight and who may believe that being big is a sign of health. The lack of awareness of the child's risk may particularly affect a parent during the time of the adiposity nadir (ie, the preschool and early school-age years when children are most lean), when early intervention to improve energy balance might yield the most benefit. Measurement of the child's height and weight and determination of BMI for age is important at all ages to identify the child who has overweight or obesity or is gaining weight more rapidly than expected; it is especially critical during early childhood when outward appearances may be most unreliable. Seeing change in percentiles is particularly helpful to differentiate children who may be healthy and grow steadily along a higher BMI curve, such as those 5% at the 95th percentile who are naturally in the high BMI range and are not adversely affected in their overall health.

Pathophysiology

Understanding of the pathophysiology of obesity continues to evolve. Certain neurohormones affect appetite, satiety, and the balance between fat storage and energy production. Ultimately, obesity results when energy intake exceeds expenditure. Historically, the storage of excess calories was an advantage to our ancestors who faced intermittent food shortage; however, this predisposition to store excess calories has contributed to increasing rates of obesity in our current setting in which the environment provides ubiquitous highly palatable, high-calorie, convenient foods and limited opportunities for physical activity.

It is known from studies of twins and family networks that susceptibility to obesity is influenced substantially by genetics; however, the magnitude of recent increases in obesity rates is suggestive of an interaction between genetic susceptibility and an obesogenic environment that facilitates unhealthy behaviors. National surveys indicate that individuals in the United States are consuming more calories now than they were decades ago. This trend is most related to increasingly widespread and easily available calorically dense foods in larger portions than ever before. A smaller but also important contribution of the population weight gain comes from less physical activity and more sedentary lifestyles. The reasons for this are myriad and include changes in transportation patterns, shifts in the workforce to jobs that involve less manual labor, and automation of household work. Children in particular have fewer opportunities for activity because of safety concerns; work habits of parents; the availability of television, computers, tablets, and smartphones; and reduced availability of physical education in school and after-school programs.

Differential Diagnosis

Most children who present to a physician with excess weight have primary obesity resulting from genetic susceptibility combined with an imbalance of caloric intake and activity levels. Only a small proportion of children have another cause, such as hypothyroidism, although many parents or guardians may initially inquire about another etiology. A thorough history, including review of systems, physical examination, and evaluation of growth parameters, helps confirm primary obesity in most cases. Whereas the child with primary obesity tends to have normal or increased height for age, the child with another etiology, such as hypothyroidism, typically is shorter than normal or has a delayed rate of linear growth. Certain genetic syndromes, such as Prader-Willi syndrome, pseudohypoparathyroidism, Bardet-Biedl syndrome, and Laurence-Moon syndrome, are associated with obesity. However, a child with any of these syndromes has other findings, such as developmental delay, dysmorphic features, and short stature, that are usually identifiable during the physical examination. Although initially another medical cause of weight gain may be lacking, evidence exists that weight gain can be exacerbated by an acquired diagnosis, such as sleep apnea, that manifests as a complication of obesity.

Evaluation

History

The history should include the age of the child, parental weight, and lifestyle information (Box 155.2). Knowledge of a child's birth weight and gestational age may be helpful. Term neonates weighing more than 4 kg (9 lb) are at increased risk of obesity. Preterm status is also a risk factor for subsequent obesity, possibly related to early metabolic effects of rapid catch-up weight gain after birth. Exclusive formula feeding may be a risk factor for obesity. A diet history, such as the 24-hour recall method or, alternatively, use of screening questions filled out by the parent or guardian in the waiting room, can be helpful to understand the dietary factors contributing to the child's overweight status, as well as to identify areas for potential change. Additionally, a history of signs or symptoms of complications of obesity should be elicited. For example, a teenager may complain of hip or knee pain

Box 155.2. What to Ask

Obesity

Open-Ended Questions to Engage Lifestyle and Family Changes Include

- What concerns do you have about your child's health? How do you feel about your child's weight?
- How has the current weight affected your child's life (eg, teasing, difficulty exercising or sleep)?
- What are you and your family already doing to support healthy habits for eating and activity?

Specific Probes to Learn More About the Child's Usual Daily Activities and Home Environment Include

- Who cares for your child during the day? (Home-based child care provided by grandparents or other family members is associated with increased risk of overweight.)
- How often does your child get to be physically active (eg, recess, physical education class, after school, on weekends)?
- Where are opportunities to add more activity (eg, to or from school, on weekends, playing sports or recreation, with parents)?
- How much time does your child spend in front of a screen, whether watching television or using a telephone, tablet, or computer? What are family guidelines for screen time? What media devices are in the child's bedroom?
- On a typical day, starting first thing in the morning, what does your child eat?
- How often does your family eat meals together? How often do you eat fast food or go out to eat?
- Who does the shopping and food preparation? Does the person who shops for food worry about food running out at home before there is money to buy more?
- How often does the child drink milk and water? How often does the child drink soda or juice drinks?
- What time does your child go to sleep and wake up? Does your child snore? Is your child rested during the day?

Questions to Set a Mutual Agenda

- What are some things you and your family would like to change for healthier eating and activity?
- Who might support you and your family in making changes?

Some Additional Questions for the Older Child or Adolescent

- Have you tried to lose weight before? How?
- Are you depressed?
- Have you participated in fad dieting? Fasting? Laxative use? Diuretic use?
- Have you used drugs, whether illicit, over the counter, or prescription, to lose weight?
- Have you used nutritional supplements for weight loss?
- Have you ever binged? Purged?
- Do you use tobacco? Alcohol?

suggestive of slipped capital femoral epiphysis (SCFE). The child may have a history of snoring, or apneic pauses followed by gasping for breath during sleep, and daytime sleepiness indicating obstructive sleep apnea (OSA). A history of irregular menstrual periods is useful in evaluation for polycystic ovary syndrome. A mental health history, including depression and anxiety symptoms, disordered eating, and history of bullying, is important to obtain. The family history, especially information on familial obesity, diabetes, hypertension, and early cardiac death, offers clues to the risk of obesity complications. Finally, a social history, including family social stressors, substance use, poverty, and food insecurity, is important to gauge the child's risks and the family's need for support to address obesity concerns.

Physical Examination

The accurate measurement of height and weight using appropriate equipment and plotting growth parameters on a BMI chart should be essential components of every well-child visit. For the child 2 years and older, the revised 2000 growth curves developed by the National Center for Health Statistics enable the physician and other health professionals to evaluate BMI for age relative to other children of the same sex. Before age 2 years, the World Health Organization weight-for-length curves should be used to assess proportional growth. Both sets of growth curves are available at www.cdc.gov/growthcharts. The child also should be examined for any dysmorphic features suggestive of an underlying genetic syndrome.

The physician should assess for potential complications of obesity when examining a child with overweight. Although many complications of obesity do not manifest until adulthood, the child with overweight is at risk for several conditions, including hypertension, hyperlipidemia, type 2 diabetes, nonalcoholic fatty liver disease, OSA, and orthopedic problems. Blood pressure should be accurately measured with an appropriate-sized cuff (larger cuffs are needed for youth with overweight) and compared with age-based standards. The skin should be examined for striae and acanthosis nigricans, the velvety pigmented lesion commonly found on the neck or axilla, which is associated with insulin resistance in children with overweight. Skin findings of hirsutism and acne in the adolescent girl with obesity may be indicative of polycystic ovary syndrome. The musculoskeletal examination should assess joint alignment and range of motion for Blount disease (ie, severe tibial bowing), SCFE, or other degenerative joint diseases. Tanner stage should be assessed for evidence of premature puberty.

Laboratory Tests

One-third to one-half of children with obesity have evidence of metabolic syndrome, a cluster of traits that includes hyperinsulinemia, obesity, hypertension, and hyperlipidemia. The higher the BMI for age, the greater the risk for metabolic complications. Laboratory studies to evaluate for potential complications of obesity are recommended starting at age 10 years, or earlier if specific concerns exist, such as severe obesity (ie, >99th percentile BMI for age) or a strong family history of type 2 diabetes or hyperlipidemia. Children age 10 years or older with a BMI above the 95th percentile (and those with BMI >85th percentile with family or other risk factors) are recommended to undergo fasting glucose and a fasting lipid panel. Some experts also recommend screening for fatty liver disease with an alanine transaminase test. The fasting glucose and/or the hemoglobin A_{1c} can help screen for diabetes or prediabetes. If results are abnormal, these tests should be repeated to confirm

diagnosis. Higher rates of nutritional deficiencies reported among youth with overweight include vitamin D, calcium, and iron; thus, screening for these should be considered based on dietary history and other risk factors.

If a genetic condition is suspected, an evaluation by a geneticist is indicated for high-resolution karyotype and other genetic tests, as directed by the suspected syndrome. For rare cases in which an underlying endocrine disorder is suspected, thyroid function studies or cortisol levels may be considered.

The child with a history of sleep-disordered breathing should be referred for a sleep study.

Imaging Studies

Radiologic studies are indicated when orthopedic complications of obesity, such as Blount disease or SCFE, are suspected. Echocardiography for evaluation of ventricular hypertrophy is a consideration in the child with long-standing hypertension, which is suggestive of left ventricle involvement, or OSA, which is suggestive of right ventricle involvement.

Box 155.3. Recommended Stages of Obesity Treatment

- Stage 1: *Prevention plus:* Initial treatment in the primary care office focuses on behavioral strategies for eating and activity changes to address causes of energy imbalance.
- Stage 2 (if no improvement within 3–6 months after stage 1): *Structured weight management* involving specific targeted goal behaviors for eating, activity, and reducing sedentary time; should include self-monitoring in the office or another setting for individual or group treatment.
- Stage 3 (if no improvement within 3–6 months after stage 2): *Comprehensive multidisciplinary management* in a pediatric weight management center or equivalent program.
- Stage 4 (for patients with body mass index >99th percentile or more severe comorbidities): *Tertiary care intervention* in a tertiary care facility that oversees more targeted medical weight loss and may offer surgical approaches.

Adapted with permission from Spear BA, Barlow SE, Ervin C, et al. Recommendations for treatment of child and adolescent overweight and obesity. Pediatrics. 2017;120(S4):S254–S288.

Management

Because not every child with obesity progresses to obesity in adulthood, a staged approach is recommended in managing childhood obesity. The pediatrician's first task is to help prevent obesity through identifying risk and using patient-directed counseling to promote healthy target behaviors and avoid unhealthy ones. Risk is largely determined by the child's age and history of parental/guardian obesity; however, race/ethnicity may also play a role. The child younger than 3 years with obesity but without an obese parent is at low risk for future obesity. These children should be monitored but, for the most part, do not require intervention. Between the ages of 3 and 5 years, parental obesity substantially increases the risk of a child having obesity as an adult. The chance of adult obesity in a preschool-age child with obesity with at least 1 parent with obesity is above 60%. In the older child, the child's own status of obesity is an increasingly important predictor of obesity in adulthood, regardless of whether a parent is obese. The probability that a child older than 6 years and with overweight will have obesity as an adult is 50%, regardless of parental obesity status. The child determined to be at high risk for future obesity requires close surveillance and intervention by the physician.

After a child has been identified as overweight, the physician is advised to follow the recommended stages of obesity treatment as shown in Box 155.3.

The core of child obesity treatment focuses on behavior and lifestyle modification, the aims of which are to improve health through increasing fitness, decreasing metabolic complications, and reducing or stabilizing BMI. The goal of treatment is sustainable and appropriate healthy eating and physical activities that do not result in disordered eating or inappropriate body image. Throughout assessment and management of obesity, the primary care physician should use supportive, nonstigmatizing language (eg, avoiding the terms "obese" and "obesity" and instead emphasizing "health" and "balance"). The physician should help families work together on physical fitness and overall health rather than focusing only on weight or body size. Involvement of the entire family in supporting healthy behaviors is necessary; the child who feels stigmatized or singled out within the family because of the child's weight may do worse overall with future weight-related health behaviors. Additionally, the physician should monitor children and teenagers for inappropriate focus on weight or engaging in unhealthy weight loss practices, including laxative abuse, induced vomiting, and fasting (see Chapter 64).

The initial weight change goal in caring for the prepubertal child with overweight is slowing weight gain or maintaining weight during normal linear growth. If more advanced treatment is indicated, the goal may include weight loss; however, loss of not more than 0.5 kg (1 lb) per month is recommended for children aged 2 to 5 years. Youth aged 12 to 18 years (or postpubertal individuals) may start at any of the 4 treatment stages, depending on severity and readiness to change. Initial treatment goals for children older than 5 years may be slowed weight gain or weight loss, with weight loss not more than 0.9 kg (2 lb) per month. As a quaternary intervention, surgical treatments for obesity are increasingly available for teenagers in select medical centers. Based on the latest policy guidance from the American Academy of Pediatrics (AAP), primary care pediatricians should recognize that severe obesity is a high-risk medical condition that is unlikely to resolve without intervention. Pediatric providers should refer patients who have severe obesity with comorbid conditions to comprehensive programs where surgery could be considered.

The physician can be most successful and efficacious in managing obesity by individualizing recommendations to the specific child and family and helping the child and family access available community resources. Motivational interviewing techniques can be helpful in determining and promoting a family's readiness to make changes to address weight concerns (Box 155.4). For the family that may not be ready to make changes, the physician can focus more on

Box 155.4. Brief Motivational Interviewing Approach to Management of Obesity in the Pediatric Patient

Goal: Through nonjudgmental questions and reflective listening, elicit a realistic plan for addressing the child's weight/health consistent with the family's values and goals.

Use: Basic motivational interviewing skills or OARS:

- O: Open-ended questions (eg, those starting with "How," "What," or "Tell me about . . .")
- A: Affirmations (eg, "You are already doing a good job with . . .")
- R: Reflections (eg, "It sounds as though you would like some help with changing . . .")
- S: Summaries (eg, "Let me see if I can summarize our discussion and plans between now and the next visit . . .")

Steps: Basic approach in 15 minutes

1. Assess BMI, inform parent or guardian and/or patient, elicit response.
   "Your child's BMI (ie, balance of weight to height) is in a range in which we start to be concerned about extra weight causing health problems. What concerns, if any, do you have about your child's weight?"
2. Set agenda: Assess what the parent or guardian and/or patient has already done, those individuals' goals for change, and possible target behaviors (Box 155.2).
3. Assess motivation and confidence to make the changes.
   "On a scale of 1 to 10, with 10 being highest, how important are the changes we have talked about for you? Why are you an "X" (ie, number chosen by the patient or family member) and not a "Y" (ie, lower number)?"
4. Ask about ways to implement the parent's or guardian's and/or patient's plans and/or goals.
   "Who can help you with your plans? What will help you be successful? How have you been able to make a change in the past?"
5. Summarize: Review plans (including follow-up), express confidence in the family, and offer further help.
   "Let's summarize our discussion today. You have planned to ____, and this is important to you because ____. You will get some help from ____ to be successful. This sounds like a plan that can work. I know you can do it if you set your mind to it. I suggest we meet again in 1 month to check in. I look forward to hearing about how well you are doing. At that time we can discuss other ways I might be able to help, such as a referral to a nutritionist or an exercise program."

Abbreviation: BMI, body mass index.

understanding values and current barriers, ordering appropriate testing to help the family assess risk, checking in frequently, and providing encouragement while respecting autonomy. For the family that is more ready to change, the physician can actively elicit from the patient and parent what those stakeholders consider to be important and feasible lifestyle changes and how they want to go about reaching their goals.

Modifying behaviors related to food and activity is difficult, and patients and their families require ongoing support and attention from their primary care physician as well as from additional clinical and community resources as they attempt to integrate and maintain healthy habits in their lives. Engaging with the family to elicit solutions and brainstorm solutions to barriers is more likely to yield positive results than blanket advice or recommendations. Even well-intentioned clinical recommendations are unlikely to be implemented if they are inconsistent with a patient's and family's values, culture, and resources. For example, a child's participation in an after-school sports program may not be a realistic option if a family cannot afford the fees or transportation to and from the program; instead, a school-based after-school program or an evening or weekend class at a community center with the parent might be an option.

In preventing and treating childhood obesity, the physician must also recognize the gaps between knowledge and behavior. That is, understanding that good nutrition and physical activity are important does not necessarily translate into healthy eating or regular exercise. For example, a parent may know to limit fat and sugar but may continue buying quantities of processed foods because of convenience or price or because of not knowing how to prepare healthier foods. Alternatively, some families may have food insecurity or periods with inadequate food that may result in overeating inexpensive, energy-dense foods. The physician should connect such families with nutrition assistance programs (eg, Special Supplemental Nutrition Program for Women, Infants, and Children [WIC], Supplemental Nutrition Assistance Program [SNAP]). Most families need additional education on appropriate serving sizes, preparation of healthful food, interpreting food labels, and making healthy food choices to counteract the mixed messages about nutrition in the media. Because time is limited in primary care office visits, referral to a dietitian or nutrition classes through WIC can be an initial step in providing families the necessary education and planning needed for changing their eating habits. For the motivated family, a dietitian can be particularly helpful for providing ideas to plan healthful daily meals and snacks.

Because the options for actively managing childhood obesity remain somewhat limited in the primary care setting, it is critically important for the physician to be aware and take full advantage of the available treatment programs in the local area. Increasingly, successful, evidence-based programs are available to help children attain a healthier weight. To date, the most efficacious programs are moderate-intensity, family-based behavioral treatment, generally of 3 to 12 months' duration. The physician can play an active role in referring to structured treatment programs by being a knowledgeable source of information and helping families learn about and become interested in these programs. Family participation in such programs often is dependent on support and encouragement from a trusted health professional. If structured overweight treatment programs are not available in the local area, the physician can recommend and refer to structured physical activity programs, such as those at local YMCAs or community centers. Physical activity programs can help a patient improve physical fitness and lower metabolic risks related to obesity, even if such programs do not result in weight loss.

A basic set of guidelines that physicians can use to help families move toward a healthier lifestyle is included in Box 155.5. Items on this list are evidence based from the standpoint that families who have implemented these generally have children with healthier weight. Some involve fairly simple changes, such as reducing intake of sugar-sweetened beverages or switching to lower-fat milk. Other suggestions may require more knowledge or motivation to implement successfully. Many websites provide excellent educational resources for families, including the US Department of Agriculture ChooseMyPlate.gov (www.choosemyplate.gov) and *Dietary Guidelines for Americans,* which is published every 5 years (www.health.gov/dietaryguidelines); Nemours KidsHealth (https://kidshealth.org); and the Let's Move! campaign initiated by former First Lady Michelle Obama (https://letsmove.obamawhitehouse.archives.gov).

Given the complexity of managing obesity, more clinical tools and additional training for pediatric professionals are available, including the AAP Section on Obesity (www.aap.org/obesity), AAP Institute for Healthy Childhood Weight (https://ihcw.aap.org/), and *We Can!* resources from the National Heart, Lung, and Blood Institute (www.nhlbi.nih.gov/health/public/heart/obesity/wecan).

Box 155.5. Ten Guidelines to Help Families Adopt a Healthier Lifestyle

1. Learn about the child's and family's usual diet and activity pattern to elicit ideas about helpful changes in which they are interested and are capable of making.
2. Promote simple "5210" guidelines for healthy living: 5 fruits and vegetables a day, ≤2 hours of screen time, ≥1 hour of physical activity, and 0 sugar-sweetened beverages a day.
3. Encourage intake of more "natural" foods, such as fruits and vegetables (fresh or frozen). Limit processed and prepackaged foods and snacks (which have added sugar and fat that children do not need) by keeping them out of the house as much as possible.
4. Set family guidelines on recreational screen time with a goal of <2 hours a day, including television, telephones, and tablets. Keep media devices out of children's and teenagers' bedrooms. (This is easier to do if the physician helps educate about not putting them there in the first place.)
5. Promote "fitness over fatness": every individual can be active and benefits from activity, regardless of the individual's weight. Explore ways for children and families to be active as part of their daily routine, with a goal of 60 minutes a day. Find sports or activities that the child enjoys and can master.
6. Teach healthy beverages for all ages: Milk and water is all we need. For children older than 1 to 2 years, change to 1% or fat-free milk. Limit milk to 16 to 20 oz per day after age 1 year. If the parent or guardian serves juice, limit the amount to <4 oz per day for toddlers and <6 oz for older children. Limit soda to special occasions (eg, birthdays).
7. Limit eating out, especially at fast-food restaurants. A goal is once a week or less. Find easy "make at home" versions of fast food, such as homemade pizza, sub sandwiches, and lean turkey burgers.
8. Promote regular family meals cooked at home. Make family mealtime a positive experience by turning off televisions and devices and instead talking together. Share stories about the day, "highs and lows," and/or something for which each person is grateful.
9. Encourage appropriate portion sizes for family members based on need. Teach parent(s)/guardian(s) "responsive eating" and how to respond to children's hunger cues during infancy and the toddler phase. Teach the "parent provides, child decides" approach to eating for children.
10. Promote healthy sleep, including regular bedtimes and adequate sleep (10–11 hours for school-age children; 8–9 hours for teenagers). Discuss how important it is to turn off devices at least 1 hour before bedtime.

Prevention

Prevention of obesity is the best option for reversing the growing epidemic of obesity and obesity-related comorbidities. Prevention of obesity should be a priority for all physicians who care for children and should focus on 3 broad areas: anticipatory guidance starting in infancy on healthful eating, adequate sleep, minimizing screen time, and providing access to regular physical activity with an emphasis on promoting overall health; early intervention for families with children who are at increased risk for developing obesity; and advocacy for public health measures to increase opportunities for healthful eating and regular physical activity within local communities. The pediatrician can take an active role in improving obesity trends by supporting changes in school and child care institutions, communities, and national policies (see resources available through the AAP and the Institute for Healthy Childhood Weight).

Prognosis

Without intervention, average life expectancy of individuals living in the United States is currently projected to decrease because of the increasing incidence of diseases associated with obesity, such as diabetes. Poor diet and sedentary lifestyles rival smoking as a preventable cause of premature death. Children with obesity who retain obesity into adulthood are at greatly increased risk for all the complications of obesity. Evidence suggests, however, that early intervention at the family and community levels can change this trajectory. Pediatricians continue to improve rates of BMI screening and referral, and those who have had training in obesity management are even more likely to implement current recommendations. Globally, more physicians and organizations are taking an active role in preventing and managing childhood obesity, and treatment options continue to evolve and improve, including the safety of bariatric surgery for youth with severe obesity. In most communities, there is a need for greater availability of all programs addressing child obesity, from prevention to treatment; pediatricians can be effective advocates for addressing this need. Childhood obesity rates in the United States have begun to stabilize, which may be a positive sign for the future.

CASE RESOLUTION

The case study describes a girl with obesity who is at substantial risk for retaining obesity into adulthood based on her present weight and her mother's history of obesity, as well as social and economic risk factors. Strengths for the family include a caring, engaged mother who recognizes her daughter's weight as a concern and is motivated to make changes. Working with a dietitian, the mother and daughter learn about simple changes for healthy diets. They begin to plan meals and snacks that include fruits and vegetables and can be prepared in advance. The daughter starts making her own lunch each night before school. The mother changes her grocery shopping: She buys 1% milk instead of whole milk and stops buying as many cookies, chips, and soda, except as an occasional treat. A social worker helps find an after-school program at the nearby YMCA. The patient starts attending and, with some special attention from the coach, finds she enjoys basketball and decides she would like to try out for the school team next year. The mother wants to exercise more, so she and her daughter plan after-dinner walks around the track at the local high school.

Over the next 6 months, you follow mother and daughter closely. The most recent growth parameters show that the girl has maintained her weight at 59 kg (130 lb) but has grown 5 cm (2 in) to a height of 145 cm (57 in), giving her a BMI of 28. The mother has lost 2.7 kg (5 lb) during this period, and both she and her daughter are excited about continuing their new lifestyle.

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CHAPTER 156

Juvenile Idiopathic Arthritis and Benign Joint Pains of Childhood

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CASE STUDY

A 4-year-old white girl is evaluated for limp. The parents are unclear about the duration of her symptoms, although they believe she began exhibiting knee problems after she was playing with her brother 3 months previously. The parents have observed the patient to walk "like her grandmother" every morning, with marked improvement in her gait after approximately 1 hour of movement. Her activity level has remained about the same, although the morning limp limits her ability to keep up with her siblings. She has no history of rash, fever, weight loss, severe pain, or other joint involvement. On physical examination, vital signs are normal; her left knee is swollen, with a 20° flexion contracture; and the left leg is 1.5 cm (0.6 in) longer than the right leg.

Questions

1. What findings are indicative of juvenile idiopathic arthritis?
2. What is the differential diagnosis for monoarticular arthritis?
3. Which laboratory tests are important in the diagnostic workup of a child with suspected juvenile idiopathic arthritis?
4. What are the most common complications of juvenile idiopathic arthritis?
5. What other organs are involved in juvenile idiopathic arthritis?
6. What are the long-term outcomes for the patient with juvenile idiopathic arthritis?
7. What types of agents are used in the management of juvenile idiopathic arthritis?

Joint pain is a common presentation in the pediatric population, and etiologies include trauma, infection, anatomic, and chronic inflammatory arthritis, such as juvenile idiopathic arthritis (JIA). Differentiating between a benign, self-limited etiology and a potentially destructive, chronic process is critical to the preservation of growing bones and cartilage. The etiology of joint pain may be roughly divided into 2 categories: mechanical and inflammatory. Mechanical or noninflammatory causes include pes planus, hindfoot valgus, and hypermobility. Inflammatory causes can be infectious, postinfectious (ie, immune complex mediated), or autoimmune mediated. Distinguishing between mechanical and inflammatory processes and determining the necessity of a pediatric rheumatology consultation may be straightforward after obtaining a detailed history and conducting a thorough physical examination and focused laboratory investigation.

Epidemiology

Juvenile idiopathic arthritis is the most common pediatric rheumatologic disease and among the more common chronic diseases of childhood. In the United States, the estimated annual incidence is 14 per 100,000 children, and the estimated prevalence is 96 per 100,000 children. The disease can occur in all racial and ethnic profiles with variable frequencies. Juvenile idiopathic arthritis is most prevalent among whites (typically oligoarticular JIA) and least prevalent in blacks and Asians. Consistent with most autoimmune diseases, females are affected more commonly than males.

Juvenile idiopathic arthritis is typically classified based on the International League of Associations for Rheumatology system. Juvenile idiopathic arthritis is an umbrella term for a set of diverse diseases with 1 common thread: chronic idiopathic inflammation of the joint space (Table 156.1). Juvenile idiopathic arthritis encompasses all of what historically was called "juvenile rheumatoid arthritis" and "juvenile chronic arthritis." The term "rheumatoid" was removed because rheumatoid factor (RF) antibodies are absent in most children with JIA. With increased knowledge of the genetics and inflammatory pathways in each subgroup of JIA, it is likely that the JIA nomenclature will be modified to further define the disease process and increase the homogeneity of each subgroup.

Table 156.1. International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis

JIA Subtype	*Peak Age of Onset (years)*	*Number of Joints Involved*	*Type of Onset*	*Sex Predilection*
Oligoarticular	4	≤4	Insidious	Girl > Boy
RF-negative polyarticular	2–5	≥5	Insidious	Girl > Boy
RF-positive polyarticular	12	≥5	Rapid	Girl > Boy
Systemic	Any, <16	Variable	Variable	Girl = Boy
Enthesitis related	12	Variable	Insidious	Girl < Boy
Psoriatic	3	Initially ≤4	Insidious	Girl > Boy
	11	≤4	Insidious	Girl = Boy

Abbreviations: JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

Data derived from Petty RE, Southwood TR, Manners P, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol.* 2004;31(2):390–392; and Cassidy JT, Laxer RM, Petty RE, Lindsley CB. *Textbook of Pediatric Rheumatology.* 6th ed. Philadelphia, PA: Saunders Elsevier; 2011.

Clinical Presentation

Juvenile idiopathic arthritis presents with arthritis during the disease course. *Arthritis* is defined as joint edema on examination or a joint or joints with both pain on range of motion and limitation of range of motion. The onset of JIA may be insidious (eg, oligoarticular), rapid (eg, RF-positive polyarticular), or variable (eg, systemic) (Table 156.1). Adolescents 16 years and older with a new diagnosis of chronic idiopathic arthritis are considered to have adult rheumatoid arthritis, not JIA. The child with JIA may be observed to limp mostly in the mornings, have difficulty completing writing assignments, or exhibit regression of gross motor milestones. Complications of JIA, such as long-standing anterior uveitis, leg length discrepancy, and joint flexion contracture, may result in difficulties performing activities of daily living and at school. Leg length discrepancy is a product of chronic inflammation providing excess blood flow to an open epiphysis (eg, most obvious is the distal femoral epiphysis), causing premature and accelerated growth with eventual premature epiphyseal closure.

Oligoarticular JIA is the most common form of JIA, with approximately 50% of all JIA cases of this type, and peaks in the second and third years of life. It is defined by the presence of arthritis in fewer than 5 joints during the first 6 months of disease and most often involves the large joints; the knee is most commonly affected, followed by the hip. A child may present with single joint involvement. Oligoarticular JIA takes persistent and extended forms, the latter associated with a more severe disease course and mimicking adult polyarticular disease. Extended oligoarthritis remains asymmetric compared with rheumatoid arthritis, which is defined by symmetric disease. Up to 50% of children with oligoarticular JIA extend to involve 5 or more joints within several years of diagnosis (ie, extended oligoarthritis).

In addition to complications, such as leg length discrepancy and joint flexion contracture, the child with oligoarticular JIA is at increased risk for developing anterior uveitis. *Anterior uveitis* is inflammation of the anterior uveal tract and adjacent ciliary body, and it is not clear why the same types of inflammatory cells are targeting seemingly disparate targets (eyes and joints). Anterior uveitis may be a clinically silent component of the disease course in approximately 25% of all patients with oligoarticular JIA and, in a minority of affected patients, may cause blindness. Guidelines put forth by the American Academy of Pediatrics and American Academy of Ophthalmology define risk factors and ophthalmologic screening frequencies for the prevention of JIA-associated uveitis and are based on the age of onset of JIA and presence of antinuclear antibody (ANA) (Table 156.2). Screening recommendations are relevant for all children with oligoarticular, polyarticular, psoriatic, and undifferentiated JIA.

Polyarticular JIA is defined as arthritis of 5 or more joints during the first 6 months of disease and represents approximately 30% of JIA cases. The 2 peaks of disease incidence are suggestive of 2 different genetic interplays. Rheumatoid factor-negative disease is the more common subtype, often with a positive ANA test and increased risk for anterior uveitis, with a tendency to present in early childhood. Rheumatoid factor-positive disease most commonly presents in early adolescent girls with symmetric small joint disease and carries a worse prognosis in terms of joint damage. The arthritis is erosive and, if disease is uncontrolled, may result in *boutonnière deformity* (ie, proximal interphalangeal joint flexion and distal interphalangeal joint hyperextension) and *swan neck deformity* (ie, proximal interphalangeal joint hyperextension and distal interphalangeal joint flexion). Disease complications include flexion contractures, leg length discrepancy, uveitis, and temporomandibular joint arthritis.

Systemic JIA is present in 10% to 15% of patients with JIA and is associated with the greatest morbidity and mortality of all JIA subtypes. Systemic JIA lacks the autoantibody, sex, age, and human leukocyte antigen (HLA) associations seen associated with other

Table 156.2. Frequency of Ophthalmologic Examinations in Children With Juvenile Idiopathic Arthritis Based on Antinuclear Antibody Status and Age at Diagnosis[a]

Disease Subtype	*ANA*	*Age at Diagnosis (years)*	*Duration of Disease (years)*	*Risk Category*	*Frequency of Eye Examinations (months)*
Oligoarticular or polyarticular	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	N/A	Low	12
Systemic (eg, fever, rash)	N/A	N/A	N/A	Low	12

Abbreviations: ANA, antinuclear antibody test; N/A, not applicable; +, positive; –, negative.

[a] Recommendations for follow-up continue through childhood and adolescence.

From Cassidy J, Kivlin J, Lindsley C, Nocton J; American Academy of Pediatrics Section on Rheumatology, Section on Ophthalmology. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics.* 2006;117(5):1843–1845.

JIA subtypes. It is characterized by fever, rash, lymphadenopathy, hepatosplenomegaly, and serositis. Classically, fevers are quotidian or daily in pattern and are accompanied by a migratory rash that consists of discrete salmon-colored macules seen predominantly on the trunk and proximal extremities (Figure 156.1). If arthritis is among the presenting symptoms, pain is worse during the febrile period. The arthritis is typically polyarticular, affecting large and small joints, and occurs within the first 6 months of symptoms. Patients are often initially categorized as "fever of unknown origin" because arthritis may be minimal or, more often, absent at time of presentation.

Macrophage activation syndrome is a rare but life-threatening complication of systemic JIA. Patients present with hepatosplenomegaly, lymphadenopathy, and purpura and may progress to multiorgan failure. A relative decrease in inflammatory markers (eg, erythrocyte sedimentation rate [ESR]) is observed in macrophage activation syndrome, which is in contrast to an elevation of these markers when systemic JIA exacerbates during disease exacerbation as liver and bone marrow function deteriorates. Treatment involves steroids and immunosuppressive therapy. In patients with systemic JIA, triggers to macrophage activation syndrome include viral infections and addition or change in medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, and etanercept.

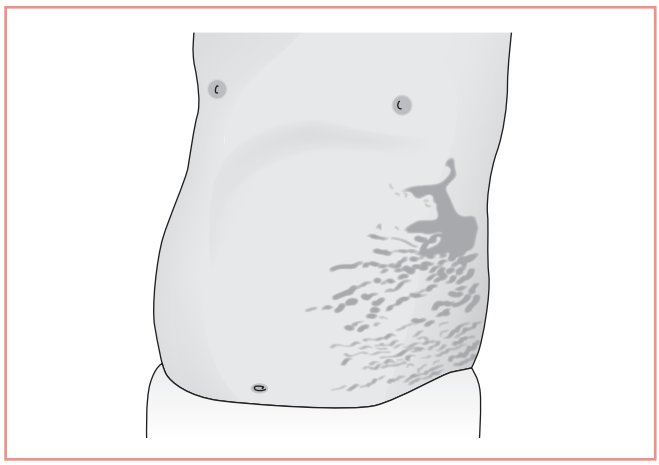

Figure 156.1. Salmon-colored rash seen in systemic juvenile idiopathic arthritis with Koebner phenomenon.

Enthesitis-related arthritis is characterized by typically lower extremity arthritis and inflammation of the insertions of tendons, ligaments, fascia, and joint capsule to bone (ie, *enthesitis*). Unlike oligoarticular and polyarticular JIA, in which autoantibodies are frequently present (eg, ANA, RF), enthesitis-related arthritis is generally seronegative with a strong association with HLA B27. Enthesitis-related arthritis most likely represents the earliest clinical stage of spondylarthritis, which is defined by inflammatory axial disease. Juvenile ankylosing spondylitis is an example of a spondylarthritis and generally affects boys aged 8 years or older. Extra-articular symptoms include anterior uveitis, which is acute and painful, in contrast with uveitis seen in oligoarticular and polyarticular arthritis, which is initially asymptomatic.

Psoriatic arthritis occurs in patients with chronic arthritis and psoriasis or those who meet 2 of the following criteria: dactylitis, nail pitting or onycholysis, and first-degree relative with psoriasis. The age at onset is biphasic, occurring at 3 years and 11 years of age. Clinical presentation of the younger cohort is similar to oligoarticular JIA, with the exception of higher frequencies of small joint involvement and dactylitis, with a sausage-like appearance of the digit. The older cohort resembles adult psoriatic arthritis and is characterized by axial skeletal involvement and enthesitis. The arthritis, which is

asymmetric, may present before the psoriatic rash, making diagnosis difficult. Similar to polyarticular JIA, the biphasic nature of psoriatic arthritis is suggestive of different genetic contributions. Up to 17% of patients have asymptomatic uveitis, similar to ANA-positive oligoarticular JIA, and require routine slit-lamp examination for diagnosis.

Differential Diagnosis

The differential diagnosis for joint pain in children is vast, including infectious, oncologic, immunologic, and autoimmune etiologies, and the pain can be characterized as self-limited or chronic based on a targeted history and thorough physical examination (Table 156.3) (Box 156.1). Joint pains of childhood may be self-limited in nature and include growing pains, postinfectious arthralgia, and pain amplification as well as mechanical abnormalities (eg, hypermobility syndrome) as causal.

Growing pains are a benign cause of pain in children and usually resolve within 1 to 2 years of onset (see Chapter 116). *Growing pains* are characterized by nocturnal pain without objective musculoskeletal manifestations. The pain generally is localized to the bilateral lower extremities and is relieved by massage, heat, or NSAIDs. The family history often is positive for growing pains. Additional workup is required in the patient with systemic symptoms (eg, fevers, weight loss), persistent pain during the day, objective musculoskeletal examination abnormalities, limping, or unilateral pain. *Osteoid osteoma* is a benign prostaglandin-producing bone tumor that typically involves the lower extremity, most commonly the proximal femur, and less commonly includes spinal involvement. Symptoms include unilateral, progressive pain that is worse at night, is unrelated to activity, and is improved with NSAIDs (ie, prostaglandin inhibitor). Physical examination may reveal point tenderness,

Table 156.3. Differential Diagnosis of Joint Pain in Children

Monarthritis	*Polyarticular Arthritis*	*Positive Systemic Features*	*Arthralgia*
		Infectious	
Septic arthritis Osteomyelitis Lyme disease	Lyme disease	Bacterial infections (eg, Lyme, TB, gonococcal, *Brucella*) Viral infections (eg, parvovirus, EBV, hepatitis B) Parasitic infection (eg, malaria)	Lyme disease Septic arthritis
		Autoimmune	
Oligoarticular JIA	Polyarticular JIA Connective tissue disease[a] Inflammatory bowel disease–associated arthritis	Systemic JIA Connective tissue disease[a] Inflammatory bowel disease–associated arthritis	Polyarticular JIA Inflammatory bowel disease-associated arthritis
		Oncology	
Malignancy (ALL)	Malignancy	Malignancy (eg, neuroblastoma)	Not usually present. Bone pain more likely
		Immunologic	
Reactive arthritis	Reactive arthritis Poststreptococcal arthritis Immunodeficiency-related arthritis Chronic recurrent multifocal osteomyelitis	Reactive arthritis Acute rheumatic fever Chronic recurrent multifocal osteomyelitis	Reactive arthritis Poststreptococcal arthritis Immunodeficiency-related arthritis
		Other	
Trauma Osteonecrosis Hemarthrosis (bleeding disorder)	Hemarthrosis if multiple joints affected	Not present	Hypermobility Osteochondrosis Pain amplification Growing pains Legg-Calvé-Perthes disease Slipped capital femoral epiphysis

Abbreviations: ALL, acute lymphoblastic leukemia; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis; TB, tuberculosis.

[a] Systemic lupus erythematosus, mixed connective tissue disease, sarcoidosis, juvenile dermatomyositis, Henoch-Schönlein purpura.

Box 156.1. Diagnosis of Juvenile Idiopathic Arthritis

- Systemic: arthritis + patterned fevers, rash, general malaise, and elevated inflammatory markers
- Oligoarticular: arthritis affecting ≤4 joints
- Polyarticular: arthritis affecting >5 joints
- Enthesitis related: arthritis + enthesitis, with or without human leukocyte antigen B27
- Psoriatic: arthritis + psoriasis *or* arthritis + dactylitis, nail abnormalities, family history of psoriasis

edema, or muscle atrophy. Diagnosis is made using a plain radiograph or, in select cases, computed tomography.

Mechanical or non-inflammatory causes of joint pain in children may include joint hypermobility (including genu recurvatum), hindfoot valgus or pronation, and pes planus. A typical presentation of a child with mechanical causes of joint pain includes a history of pain during or after activity, relief with rest, and typical physical examination findings. Further questioning may reveal a history of pain exacerbation of the knees, ankles, and feet when the child does not wear supportive shoes during physical activity. *Benign hypermobility syndrome* is defined as generalized joint hypermobility in the absence of other connective tissue abnormality or congenital syndrome. Although approximately 8% to 20% of whites meet criteria for this syndrome, many additional white individuals have hypermobility limited to a few joints. The patient with hypermobility syndrome commonly experiences fibromyalgia (a pain amplification syndrome) and patellofemoral syndrome as comorbid conditions. Joint edema can occur but is not persistent, as in chronic inflammatory arthritis.

Joint pain that is acute in onset, monoarticular, severe in quality, and accompanied by fever is suggestive of septic arthritis, an orthopedic emergency because of the rapid cartilage destruction if treatment is delayed. Monoarticular joint pain that is localized to the periarticular region, severe in quality, and accompanied by weight loss and abnormal complete blood cell count is suggestive of malignancy, such as acute lymphoblastic leukemia. Generally, joint pain that is persistent, daily, worse in the morning, not severe in quality, and known to improve with activity is suggestive of a chronic inflammatory arthropathy, such as JIA.

Pathophysiology

The exact pathogenesis of JIA is unclear, and a monogenetic inheritance pattern has not been observed. Autoimmune diseases result from an alteration in the selection, regulation, or death of T cells or B cells, which results in an abnormal response to a particular antigen. Genetic factors increase an individual's vulnerability but are not sufficient for disease expression. Clinical manifestations are believed to result from an interplay of environmental triggers, immune mechanisms, and largely specific HLA predisposition. Multiple HLA types have been associated with the development of JIA, with early-onset oligoarticular JIA having the most distinctive HLA associations. The level of risk to family members of a child with JIA seems to be only mildly increased compared with the general population.

The hallmark of chronic idiopathic arthritis is synovial cell proliferation with synovial fluid accumulation, also called pannus. The marked expansion of cells within a closed space results in stretching of periarticular ligaments and tendons. The cells responsible for inflammation (ie, lymphocytes [mostly T cells], macrophages, and dendritic cells) are recruited from the peripheral circulation and penetrate into the synovial membrane because of factors that include proangiogenic and vasoactive proteins. An aberrant immune system produces inflammatory cytokines that are found in large numbers within the synovial membrane or fluid (eg, tumor necrosis factor [TNF], interleukin [IL]-1, IL-6), enzymes that degrade collagen and articular cartilage, and signals that activate osteoclasts and result in bone erosion.

Evaluation

History

The history should clearly delineate the duration, severity, and extent of the symptoms (Box 156.2).

Physical Examination

The patient should undergo a complete physical examination that includes a full assessment of the skin, all joints (including the temporomandibular joint), flexibility of the spine (particularly cervical and lumbosacral), and evaluation for leg length discrepancy. Specific to the pediatric examination is the consideration of normal joint hypermobility when assessing for arthritis. Comparing bilateral joints is imperative in discerning subtle flexion contracture, which is suggestive of chronic arthritis. All patients suspected of having JIA should also undergo a slit-lamp examination of the eyes. However, any girl younger than 6 years and with a positive result on ANA testing should undergo an examination as soon as

Box 156.2. What to Ask

Juvenile Idiopathic Arthritis

- Has the child ever had any swelling, warmth, or redness of joints? Which joints have been involved and for how long?
- Does the child have difficulty walking or running? If so, does it occur at any particular time of day?
- Did the pain start acutely? Has the pain been persistent, intermittent, or migratory? Does the pain wake the child up from sleep?
- Are there other symptoms present, such as fever, rash, fatigue, gastrointestinal symptoms, and weight loss?
- Is there a history of other medical problems, such as gastroenteritis, inflammatory bowel disease, or psoriasis?
- Was there a precipitating event, such as trauma?
- Has the child traveled recently or been bitten by a tick?
- Is there a family history of growing pains, hypermobility, or autoimmune disease, such as juvenile idiopathic arthritis, psoriasis, or lupus erythematosus?

possible because uveitis activity is initially silent but can be progressive. Ocular examination should be performed by a pediatric ophthalmologist or uveitis specialist. Optometric examination or in-office funduscopy are not adequate substitutes for the specialty ocular examination.

Laboratory Tests

A diagnosis of JIA is primarily based on physical examination and history. A targeted laboratory investigation helps to evaluate for other etiologies. For example, a young child presenting with monoarticular arthritis and a marked elevation in acute phase reactants (ie, ESR >100) should be evaluated for malignancy and infection. Typically, the child with oligoarticular JIA has normal acute phase reactants, with any persistent elevation considered a poor prognostic factor (Table 156.4). In the older child, evaluating for the presence of RF, anti–cyclic citrullinated peptide antibody, ANA, and HLA B27 may help with diagnostic and prognostic assessment. The most important laboratory test in the diagnostic evaluation of a young child with chronic arthritis is for ANA. A positive ANA test result helps in the risk stratification of the child for the development of JIA-associated uveitis (Table 156.2).

Imaging Studies

Imaging is used to determine the extent and severity of joint damage and help exclude other diagnoses (eg, metaphyseal lines seen in leukemia, osteoid osteoma). Conventional radiography is used in the assessment of joint damage, such as bone erosion, joint space narrowing, joint subluxation, misalignment, and ankylosis. Synovitis on ultrasonography, as measured by excess synovial fluid, synovial hypertrophy, and joint space hyperemia, is diagnostic for JIA. Magnetic resonance imaging is the standard for detecting synovitis and enables assessment of all structures for active inflammation and joint damage. Ultrasonography and magnetic resonance imaging are more sensitive (eg, for detecting synovitis) than clinical examination in the assessment of arthritis.

Management

The objective of management for JIA is to control pain and inflammation while preserving function and normal growth, development, and well-being. Physical and occupational therapy are essential to maintain function but are of limited benefit in the setting of ongoing inflammation. The American College of Rheumatology published guidelines for the management of JIA that describe initiation and monitoring of therapeutic agents, including NSAIDs, disease-modifying antirheumatic drugs (DMARDs), and biologic drugs. Nonsteroidal anti-inflammatory drugs are first-line therapy for JIA, including several available in liquid formulations (eg, naproxen, meloxicam, ibuprofen). Methotrexate, a DMARD that has been used in distinctly different and significantly lower doses than for chemotherapy, has been used successfully for decades as a second-line arthritis agent. Biologics have greatly reduced the morbidity of disease, with fewer side effects compared with previously used therapeutic agents (eg, chronic steroids). Several biologics have been approved by the US Food and Drug Administration (FDA) for specific JIA subtypes, including anti-TNF (eg, etanercept, adalimumab), anti-IL-1 (eg, canakinumab), anti-IL-6 (eg, tocilizumab), and T-cell costimulatory blocker (eg, abatacept). Medication side effects are generally well tolerated by the pediatric population. The more common and relevant side effects include gastrointestinal with NSAIDs and oral methotrexate, as well as increased number and duration of upper respiratory and skin infections with methotrexate and biologics. No current evidence exists to suggest definitively that monotherapy with biologics increases the rate of malignancy in children with JIA.

Live vaccines should not be administered to individuals undergoing treatment with systemic immunosuppression. In the absence of systemic immunosuppression, routine vaccines should be administered to all children with JIA, regardless of disease activity.

Oligoarticular JIA is usually responsive to intra-articular steroids and/or managed with NSAIDs. Local steroid therapy has been shown to induce remission in select patients and may eliminate the need for systemic medication exposure. Methotrexate, a weekly DMARD, is used in patients with persistent disease despite joint injection and/or an adequate (2- to 3-month) trial of an NSAID. Anti-TNF therapy is introduced if a patient continues to exhibit moderate to high disease activity after 3 months of DMARD, more likely in the extended-oligoarticular subtype.

Initial management of polyarticular JIA is aggressive to reduce pain, inflammation, and the potential for joint damage. The patient with mild disease activity may initially be treated with NSAIDs; however, moderate to high disease activity warrants rapid initiation of methotrexate and anti-TNF agents. In addition to systemic medications, intra-articular steroid injections are used in the patient with 1 or 2 joints with particularly high disease activity. The belief that a child will "grow out of the disease" is not correct in polyarticular JIA, and families should be made aware of this prognosis, thereby improving their understanding of risk versus benefit of medications and therapeutic interventions.

Management of systemic JIA has progressed from steroid-predominant to steroid-sparing biologic therapy, specifically IL-6 and IL-1 antagonists. Interleukin-6 and IL-1 are 2 key inflammatory proteins found in systemic JIA inflammation. Tocilizumab (IL-6 inhibitory) and canakinumab (IL-1 inhibitor) have been FDA-approved for the management of systemic JIA. Nonsteroidal anti-inflammatory drugs, methotrexate, intra-articular steroid injections, and glucocorticoids may also be part of disease management.

Table 156.4. Typical Laboratory Evidence of Systemic Inflammation in Juvenile Idiopathic Arthritis

Juvenile Idiopathic Arthritis Subtype	*Acute Phase Reactants*
Oligoarticular	Normal
Polyarticular	Elevated
Systemic	Elevated
Macrophage activation	Relative decrease
Enthesitis related	Normal/mild elevation in polyarticular type
Psoriatic	Normal/mild elevation in polyarticular type

A pediatric ophthalmologist or uveitis specialist and pediatric rheumatologist are involved in the co-management of anterior uveitis. First-line therapy includes topical glucocorticoids and dilating drops. If eye disease is refractory to topical treatment or is steroid dependent, however, DMARDs (eg, methotrexate, anti-TNF therapy) are considered.

Prognosis

Among individuals with persistent oligoarticular JIA, 75% report disease remission, whereas only 12% of those with extended subtype report remission and the remaining 13% continue to experience symptoms into adulthood. Children with polyarticular JIA experience the same remission rates as those with the extended subtype (10%–15%). Features of poor prognosis include arthritis of the hip or cervical spine, evidence of bone erosion on imaging, persistently elevated ESR with wrist or ankle arthritis in patients with oligoarticular arthritis, and RF-positive or anti-cyclic citrullinated peptide antibodies in patients with the polyarticular type. Uveitis may continue even when the arthritis is improved or in remission. In systemic JIA, systemic features such as fever and rash tend to subside during the initial months to years of the disease but may flare, as in most autoimmune diseases. Approximately 40% of children with systemic JIA follow a monocyclic disease course and eventually recover. A small proportion of children have a polycyclic course characterized by recurrent episodes of active disease interrupted by periods of remission without medications, whereas more than 50% of children with systemic JIA have a persistent disease course.

The care of a child with chronic inflammatory arthritis also requires a multidisciplinary approach involving a primary care physician, rheumatologist, physical therapist, and subspecialists with expertise in affected organs. The primary care physician plays a vital role in monitoring for potential medication side effects (eg, infection) and disease activity, as well as ensuring optimal immunization for each child. Children with JIA are no exception when monitoring for appropriate growth at well-child and -adolescent examinations. High disease activity and high steroid burden can suppress growth initially; therefore, coordination of care to ensure appropriate nutrition and physical activity is vital. Supplementation with calcium and vitamin D is beneficial to prevent osteoporosis for all patients with chronic inflammation, in particular those on chronic steroids. Disease management for patients with chronic inflammatory arthritis is a balance of optimal function, minimal complications, and improved quality of life.

CASE RESOLUTION

The girl has a presentation consistent with oligoarticular JIA based on the number of involved joints with arthritis, the chronicity of her concerns by history, and abnormal physical examination. Testing for ANA was positive, which puts her at high risk of developing anterior uveitis (younger than 6 years at diagnosis, duration of disease, positive result on ANA test). She is referred to a pediatric ophthalmologist for uveitis screening every 3 months for the first 4 years following diagnosis and every 6 months for the next 3 years, followed by yearly screening thereafter. She is also referred to a pediatric rheumatologist for assistance in managing her disease and a physical therapist to address her limitation of motion and resultant weakness.

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CHAPTER 157

Autoimmune Connective Tissue Diseases

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CASE STUDY

A 14-year-old girl has a 1-month history of severe fatigue with difficulty sleeping and nonrestorative sleep, hand swelling, generalized aches, low-grade fever, weight loss, and face and leg rashes. She has not felt well enough to go to school for several weeks and states that her fingers are stiff and she cannot type. On examination, she appears tired and does not look well. Vital signs show a temperature of 38.1°C (100.5°F), blood pressure of 138/84 mm Hg, pulse of 98 beats per minute, and respiratory rate of 22 breaths per minute. Her eyes appear puffy, and her ankles and feet are swollen. She has swelling over the joints of her fingers and reports difficulty closing buttons.

Questions

1. What patient findings are concerning for an autoimmune disease?
2. How can the clinical history and laboratory evaluation assist in determining the diagnosis and treatment?
3. What would be your differential diagnosis for the patient in the case study, and what consultants might be helpful in diagnosing and managing the patient?
4. What are the criteria for the diagnosis of systemic lupus erythematosus? Based on the case study provided, does this patient meet criteria for systemic lupus erythematosus?
5. What therapies are used in patients with autoimmune connective disorders?

Although the diseases discussed in this chapter have been called "collagen vascular diseases" and "connective tissue diseases," their etiology is the result not of a gene mutation (as is the case with collagen gene mutations in osteogenesis imperfecta) but of inflammation and damage to connective tissues, blood vessels, and other organs resulting from aberrant immune responses in individuals genetically predisposed to autoimmunity. Significant progress has been made in classifying each disease with criteria for diagnosis, including clinical and laboratory findings. Most of the diseases discussed herein have associated autoantibodies that aid in diagnosis; however, these autoantibodies have not been definitively implicated in the disease pathogenesis.

Treatment algorithms for autoimmune connective tissue disorders have been proposed by the Childhood Arthritis and Rheumatology Research Alliance (comprising pediatric rheumatologists from Canada and the United States) and the Paediatric Rheumatology INternational Trials Organisation (a European organization). Generally, treatment for these diseases, which usually includes steroids and immunosuppressive therapies, must be started early and often aggressively to prevent organ damage. Although great progress has been made in the management of juvenile idiopathic arthritis (see Chapter 156) with the new biologic therapies, many other autoimmune diseases are still managed with medications used for the past several decades. One exception is belimumab (ie, Benlysta), a B lymphocyte stimulator-specific inhibitor approved in 2011 and used to treat systemic lupus erythematosus (SLE). Although belimumab appears to help with autoimmune rashes and arthritis, it does not appear to adequately treat lupus nephritis. Still, with the advent of the biologic therapies and enzyme inhibitors, steroid sparing, targeted therapies for these autoimmune diseases are under investigation.

Evaluation for Autoimmune Disease: General Considerations

History

Generally, the rheumatologic diseases are diagnoses of exclusion and warrant consideration in the context of a comprehensive differential diagnosis. The history is important to determine if an autoimmune disease is likely and should clearly delineate the onset (eg, whether a patient had a prior illness or injury), duration (eg, continuous or intermittent symptoms), and extent of the symptoms (eg, systems involved, severity of pain, swelling) (Box 157.1).

Physical Examination

A complete physical examination should be performed. The vital signs should be measured and noted if abnormal. The full physical examination must include complete examination of the skin;

Box 157.1. What to Ask

Autoimmune Disease

- Does the patient have a sleep disturbance not explained by poor sleep environment? Has the patient experienced fatigue that interferes with normal activities? Does this fatigue extend to the weekends?
- Does the patient have a history of rash? If so, what location? Does the patient experience photosensitivity (ie, does the sun make it worse)?
- Is the patient experiencing bruising or easy bleeding?
- Are visible changes in the joints present, such as swelling, erythema, or tightening of the skin? If so, at what location(s), and what is the extent of changes?
- Are the symptoms more pronounced at specific times of day (ie, morning stiffness, morning periorbital edema, swelling of the ankles at night)?
- Has the patient experienced weakness?
- What other symptoms, such as headache, fever, and weight loss, are present?

a thorough musculoskeletal examination, including assessment of spinal flexibility and muscle strength; and a neurologic and neuropsychiatric assessment. Lymphadenopathy should be noted as well as the presence of organomegaly. The presence of edema is noted by puffiness around the eyes in the morning and pitting edema of the feet, ankles, and even up to the knee at the end of the day. Pitting edema may be indicative of renal disease.

Laboratory Tests

Generally, laboratory tests should include a complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, urinalysis, and other studies as determined by the differential diagnosis. The patient with suspected SLE should undergo an evaluation of autoantibodies, including antinuclear antibody (ANA), anti-dsDNA, anti-ribonucleoprotein (RNP)/anti-Smith (Sm), and anti-SS-A (Ro)/anti-SS-B (La). Low complement levels (resulting from consumption) are important indicators of active SLE. It is appropriate to obtain electrocardiograms (ECGs) and echocardiograms in the patient with SLE and with suspected cardiac involvement. Concern about vasculitis warrants antineutrophil cytoplasmic antibody (ANCA) testing. The renal system may be involved in many of the autoimmune diseases, and a urine protein/creatinine ratio can help quantify any existing proteinuria. Suspicion for inflammatory myopathies warrants measurement of creatinine phosphokinase, aldolase, and lactate dehydrogenase levels, and, if autoimmune myositis is suspected, myositis-specific antibodies. Magnetic resonance (MR) imaging of the muscle, electromyography, and muscle biopsy may be indicated if the diagnosis is not clear.

Imaging Studies

Radiography is helpful in the initial evaluation. Chest radiography might reveal an enlarged heart, pulmonary edema or other pulmonary lesions, or bony abnormalities. Additionally, radiographs reveal changes in the joints and help assess the acuity and chronicity of joint swelling. High-resolution chest computed tomography (CT) may show subtle changes in the lung parenchyma. Magnetic resonance imaging and MR angiography are helpful in the evaluation of central nervous system (CNS) lupus, and an MR image of the muscle may show inflamed joints in juvenile dermatomyositis (JDM).

Management

The management of autoimmune diseases is based on the diagnosis and disease severity.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is a classic autoimmune disease, with most patients having 6 or more different autoantibodies. The disorder is characterized by multiorgan system involvement and a waxing and waning course. The clinical presentation is variable and may be mild, presenting primarily with rash and arthritis. In the pediatric population, however, the presentation often is more severe, with frequent renal and other organ system involvement. Systemic lupus erythematosus can present in any organ and should be considered in any child with multiorgan system symptoms. Antinuclear antibodies are present in greater than 90% of patients with SLE but can also be seen in many other diseases. Up to 20% of the healthy population has a positive ANA but have no SLE. Other, more specific autoantibodies usually are present and may be associated with disease manifestations. Studies have shown that symptoms of SLE may be present well before the diagnosis is made, and it may take time to see the full picture. The goal of treatment is to decrease the inflammation and bring the immune system into balance.

Epidemiology

Systemic lupus erythematosus is not a common disease, but those with Hispanic, African, Native American, or Asian ancestry have an increased incidence and prevalence. Approximately 20% of cases of SLE are diagnosed in the pediatric population (ie, <19 years of age). The prevalence is approximately 6 to 18.9 per 100,000 among white females, 20 to 30 per 100,000 among black females, 16 to 36.7 per 100,000 among Puerto Rican females (13 per 100,000 for Hispanics in general), and up to 31 per 100,000 for those of Asian descent. The female to male ratio varies from 4:1 to 13:1 depending on the ethnicity of the cohort. In the 1960s, before therapy was initiated early and aggressively, children with SLE lived for approximately 2 years after diagnosis. Currently, with early recognition and therapy, the 5- and 10-year survival rates for pediatric SLE have improved to greater than 95% and 92%, respectively. Survival is affected by socioeconomic status, access to health care, educational background, racial and ethnic background, endemic infection rates, disease activity, and renal or CNS involvement. In the first 2 years following diagnosis, mortality is often associated with severe disease, and death results from pancreatitis, pulmonary hemorrhage, infection, thromboembolic disease, and active neuropsychiatric disease. More than 5 years after diagnosis, causes of mortality include complications

of end-stage renal disease, atherosclerosis, suicide, and, less commonly, active SLE or infection.

Etiology and Pathogenesis

Systemic lupus erythematosus is the prototype of autoimmune disease with multiple autoantibodies. The current hypothesis is that a genetic predisposition to SLE exists that is activated by environmental factors. The genome-wide association studies done in 2008 and expanded on in subsequent studies have identified more than 50 robust susceptibility loci of genes associated with SLE. These candidate genes are mostly involved in a variety of pathways, including immune complex processing, toll-like receptor signaling, activation of adaptive immunity, and type I interferon production. In addition, there is a clear association with deficiencies in early components of complement and SLE. This association is noted in certain consanguineous populations in which there is a high prevalence of SLE that affects young children from families with these complement defects. Environmental factors include ultraviolet radiation, viral infections (a strong association exists between SLE and Epstein-Barr virus), and drugs and chemicals.

Additionally, a well-studied immune dysregulation exists that involves the innate and adaptive immune systems. The loss of tolerance in SLE results in recognition of a self-antigen as foreign, with subsequent autoantibody production (antibodies to DNA, histones, and small RNA proteins), increase in both proinflammatory cytokines and immune complexes. Theories include the generation of self-antigens on cell surfaces following apoptosis; abnormalities of innate immunity, including toll-like receptors; abnormalities of all arms of the adaptive immune system, including antigen-presenting cells, T cells, and B cells; and abnormal regulation of interferon-α.

The increased incidence of SLE in females has been attributed in part to an estrogen hormonal effect. Most children with SLE present around the time of puberty, which suggests that the increased estrogen may exacerbate the disease process. Additionally, there may be factors on the X chromosome that predispose to the lupus pathogenesis. For example, men with Klinefelter syndrome (XXY) have a 14-fold increased risk of developing lupus compared with XY men, whereas women with Turner syndrome (XO) have a decreased risk of lupus.

Clinical Presentation

In 1982, criteria for the diagnosis of SLE were established by the American College of Rheumatology and modified in 1997 to include antiphospholipid (aPL) antibodies. To fulfill the criteria for a diagnosis of SLE, 4 of the 11 clinical and laboratory findings must be present at some point during the disease. The criteria are approximately 95% specific and sensitive for diagnosis (Box 157.2). At the 2017 annual European Congress on Rheumatology, weighted criteria were proposed and are being evaluated to more specifically diagnose SLE.

Usually, patients present with constitutional symptoms such as fever, fatigue, and weight loss. Often, a history is present of a photosensitive rash and swelling of the joints. Additionally, the patient may exhibit systemic inflammation with lymphadenopathy and hepatosplenomegaly.

Box 157.2. Systemic Lupus Erythematosus Criteria for Diagnosis

Four of the following 11 clinical and laboratory findings are required for diagnosis:

- Butterfly rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Nonerosive arthritis
- Pleurisy or pericarditis
- Renal disorder
- Seizures or psychosis
- Hematologic disorder
- Positive autoantibodies (anti-dsDNA, anti-Smith, or antiphospholipid antibody/lupus anticoagulant)
- Positive antinuclear antibody

Adapted with permission from Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997;40(9):1725.

In the pediatric population, more than 80% of patients have renal involvement at onset or at some point in the disease.

Mucocutaneous Involvement

Although the butterfly rash is strongly associated with SLE, only 60% of patients have this type of rash at onset, although up to 85% will have the butterfly rash at some point in their disease. This rash is usually photosensitive, crosses the nose, and is present on both cheeks but spares the nasolabial folds. Other photosensitive rashes exist, including palpable purpura. Less common in the pediatric population is the discoid rash, which involves the dermis and can result in scarring. The discoid rash most often occurs in blacks. Approximately 10% to 30% of patients will have painless oral and nasal ulcers. Raynaud phenomenon is noted in 15% to 20% of children, but it is not specific for SLE.

Musculoskeletal Involvement

Often from onset and throughout the course of the disease, most patients with SLE will experience arthritis, arthralgia, or tenosynovitis. Typically, the arthritis is a symmetric polyarthritis affecting large and small joints, especially the metacarpophalangeal and proximal interphalangeal joints of the fingers. The arthritis is nonerosive and usually responds to treatments administered to control other aspects of the disease. Myalgia, and more rarely myositis, occur in SLE and are usually responsive to treatment. Some patients, however, develop a myopathy related to steroid treatment itself. Up to 20% of patients with SLE may develop a secondary pain amplification syndrome (ie, fibromyalgia).

Renal Involvement

After skin and joints, the organ system most frequently involved in SLE in the pediatric population is the kidney. Approximately 50% of patients present with lupus nephritis, but by the end of the first year following diagnosis, 80% to 90% of patients with SLE manifest

renal involvement. Treatment and prognosis is based on the histologic classification of nephritis as established by the World Health Organization (WHO) using renal biopsy (class I–VI) (Box 157.3). The clinical markers (ie, proteinuria, hematuria, creatinine level) may not correspond to histologic classifications, but often WHO classes III and IV are associated with hypertension and impaired renal function and are managed with high-dose steroids and immunosuppression. The patients with WHO class III, IV, or V may also present with peripheral edema requiring steroid therapy. With more aggressive and consistent treatment, overall survival for patients with renal involvement has improved, with markedly increased 5- and 10-year survival rates.

Neuropsychiatric Involvement

Often, neuropsychiatric manifestations are underappreciated because patients often present with headaches, poor school performance, and features of depression. Involvement of the CNS or peripheral nervous system may be present in 20% to 95% of patients with SLE (thus, the term "neuropsychiatric SLE"). Headaches are the most frequent presentation, with a *lupus headache* defined as a migraine-like, unremitting headache requiring narcotic analgesics. Headaches refractory to treatment can be indicative of active CNS vasculitis, increased intracranial pressure, or cerebral vein thrombosis. Thrombotic events in the CNS or elsewhere often are associated with aPLs in patients with lupus, and a full workup with urgent imaging is indicated. In these cases, MR angiography often shows vasculitis or evidence of bleeding or ischemia. Psychosis manifested by visual and tactile hallucinations may be present in 30% to 50% of patients. Hallucinations are usually visual but may also be auditory. Imaging studies in patients with hallucinations may be normal, but often autoantibodies are found in the blood or spinal fluid. Psychosis in isolation warrants consideration of the secondary effects of glucocorticoids. More difficult to delineate is cognitive impairment, which may present as a broad range of symptoms from difficulty concentrating to confusion and coma. Other, less common neurologic symptoms include seizures, movement disorders (eg, chorea), and cranial nerve abnormalities. Imaging studies are an important part of the workup and may show vasculitis, hemorrhage or clot, or demyelination; alternatively, such studies may be normal in antibody-mediated CNS disease.

Hematologic Involvement

Anemia, thrombocytopenia, and lymphopenia may be present in 50% to 75% of patients. During active disease, a patient often has a normochromic, normocytic anemia typical of anemia of chronic disease.

Box 157.3. Lupus Nephritis: World Health Organization Classification

Class I: Normal or minimal mesangial proliferation
Class II: Mesangial proliferation
Class III: Focal proliferative, <50% glomeruli
Class IV: Diffuse proliferative, >50% glomeruli
Class V: Membranous, subepithelial immune deposits
Class VI: Sclerosing without active disease

The Coombs test is positive in 30% to 40% of patients, but only 10% to 15% of patients with SLE have significant hemolysis. Thrombocytopenia is present in 15% to 45% of patients. Patients with chronic autoimmune idiopathic thrombocytopenic purpura (AITP) and Evans syndrome (ie, AITP and Coombs-positive anemia) with a positive ANA test are more frequently diagnosed with SLE. Lymphopenia is thought to represent a general marker of disease activity.

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome (APS) is a prothrombotic state that is secondary to acquired autoantibodies, including anticardiolipin (aCL) antibodies, the lupus anticoagulant (LAC; usually measured by partial thromboplastin time mixing studies or the dilute Russell viper venom time), and β2-glycoprotein I (β2GPI, apolipoprotein H). These aPL antibodies are directed against phospholipids that are found in cell membranes throughout the body and, as such, are composed of many different antibodies with different epitopes. The most common aPL antibodies are the aCLs and the LAC. The term "lupus anticoagulant" is a misnomer, however, and the condition is so called because the phospholipid-dependent partial thromboplastin time cascade is prolonged in the presence of aPL antibodies. In contrast, the affected patient is at risk for a thrombotic event because the aPL antibodies bind to the epithelial membranes of blood vessels and activate clotting mechanisms. Antiphospholipid antibodies alone may be associated with infection, malignancies, or autoimmune states; however, they are usually benign and transient. A risk of thrombosis is present with high titer aCL immunoglobulin (Ig) G or IgM, LAC positive status, or high titers of IgG or IgM β2GPI antibodies.

Antiphospholipid antibody syndrome can occur as a primary disease without an associated autoimmune disease but most often occurs patients with SLE. In children with SLE, aCL, β2GPI, occur in 44%, 40%, and 22%, respectively. The child may present with arterial, venous, or small vessel thrombosis. Although only 16% to 36% of children with aPL antibodies are at risk for a thrombotic event, those with LAC positivity have a 28-fold increased risk. The most frequent thrombotic event is deep vein thrombosis, followed by cerebral sinus vein thrombosis, portal vein thrombosis, thromboses in the deep veins of the upper extremities, and superficial vein thromboses. Thrombocytopenia and hemolytic anemia may also be secondary to aCL binding to the red cell and platelet membranes. Because children are at low risk for thrombosis, most are monitored without specific therapy. Some physicians start hydroxychloroquine sulfate (eg, Plaquenil, Quineprox), which has been shown to decrease erythrocyte aggregation on the endothelium. Low-dose aspirin is often used as an anticoagulant, but its efficacy is in question. In the patient with a documented thrombotic event, anticoagulation (eg, warfarin [Coumadin, Jantoven]) is used, but low-molecular-weight heparin (eg, Enoxaparin) or another anticoagulant can also be used, often for 6 months or longer.

Catastrophic APS is of concern because this is a life-threatening disease process in which 3 or more organ systems develop small vessel occlusions within 1 week in association with aPL. These children present with adult respiratory distress syndrome, hypertension, renal failure, and multiple other organ system involvement requiring intensive care therapies. Immediate and aggressive therapy,

including anticoagulation, plasmapheresis, and corticosteroids, is necessary to reverse the thrombotic storm, but the mortality rate is still high (up to 50% in some reports). After recovery from catastrophic APS, lifelong anticoagulant therapy is indicated.

Cardiac Involvement

Pericarditis is not uncommon in SLE (15%–25% symptomatic; however, ECG changes are noted in up to 68%), and the affected patient may be asymptomatic. The myocardium and pericardium may also be involved, as well as the valves (ie, aortic, tricuspid, mitral) with sterile verrucous vegetations or Libman-Sacks endocarditis. Libman-Sacks endocarditis may be associated with aPLs and increase the risk for subacute bacterial endocarditis. A patient may present with chest pain that is worse when lying down or taking a deep breath. Chronic inflammation is associated with an increased risk of premature arthrosclerosis, and myocardial infarction is a leading cause of death in young adults with SLE.

Pleuropulmonary Involvement

The lungs may be involved in 25% to 75% of patients with SLE, with higher numbers noted by abnormal findings on pulmonary function tests (PFTs) in an otherwise asymptomatic patient. Pleurisy is the most common manifestation and may be associated with pericarditis. Symptoms include chest pain, orthopnea, and dyspnea, and a chest radiograph may show a pleural effusion (frequently unilateral). The patient may present with pleuritic chest pain and respiratory distress associated with acute lupus pneumonitis or pulmonary hemorrhage or may have a more indolent course with interstitial lung disease and shrinking lung syndrome (ie, loss of lung volume resulting from diaphragmatic dysfunction or phrenic nerve dysfunction). Pulmonary hypertension may be insidious and is a life-threatening complication of pulmonary involvement. Because of the disease and medications, opportunistic infections are also problematic. Imaging studies, especially a high-resolution chest CT, as well as PFTs are indicated if pulmonary disease is suspected.

Gastrointestinal Involvement

Gastrointestinal (GI) involvement may be difficult to diagnose and differentiate from adverse effects from medication. The GI system is involved in approximately 20% of patients with SLE. During active inflammation, a patient often has hepatosplenomegaly. High transaminase levels are suspicious for lupoid hepatitis. Symptoms may include abdominal pain and diarrhea. Underlying pathology may be lupus peritonitis, enteropathy, or, in the setting of copious diarrhea, protein-losing enteropathy. Severe abdominal pain is seen with mesenteric vasculitis. Celiac disease has been associated with SLE and should be considered in the setting of severe weight loss. Pancreatitis may occur in association with active lupus or with steroid use and often presents with abdominal pain, nausea, and vomiting.

Endocrine Involvement

Antithyroid antibodies are common in SLE (up to 35%), and 10% to 15% of patients develop hypothyroidism. Thyroid-stimulating hormone should be checked annually in the patient with SLE. Diabetes can be associated with SLE, but more frequently, diabetes is induced by corticosteroid treatment. Growth failure is a consequence of active disease and corticosteroid therapy. The potential exists for a delay in puberty and menstrual abnormalities and, rarely, autoimmune ovarian failure. Ovarian failure may also occur as a result of immunosuppressive treatment with cyclophosphamide.

Ocular Involvement

Active disease with retinal vasculitis may cause cytoid bodies (cotton-wool spots) noted on retinal examination. Antiphospholipid antibodies may cause retinal vein occlusion and vision loss. Episcleritis and scleritis may occur. Keratoconjunctivitis sicca may occur in the patient with secondary Sjögren syndrome.

Autoantibodies in Systemic Lupus Erythematosus

Autoantibodies are the hallmark of SLE, and most patients have more than 6 autoantibodies (Box 157.4). A positive ANA is found in nearly all patients, but this is not specific for or associated with a certain disease manifestation. The antibodies of SLE are directed against histone, nonhistone, RNA-binding, cytoplasmic, and nuclear proteins. These include anti-DNA (65%–95%), anti–RNA-binding proteins, and anti-U1RNP (27%–34%) and anti-Sm antibodies (32%–34%). Anti–SS-A and anti–SS-B antibodies (27%–33%) are seen less frequently but are associated with skin disease and neonatal lupus. Anticardiolipin (19%–87%) and the LAC (10%–62%) are the most common aPLs.

Management

Treatment of children and adolescents with SLE must be started early to prevent organ damage. Treatments must be tailored to the symptoms, but young patients are reported to have more severe disease and often require aggressive therapy. A summary of treatments used in pediatric lupus and their most common adverse effects are enumerated in Table 157.1.

Vasculitis

Vasculitis is an inflammatory process involving the blood vessel wall; thus, any organ system may be involved. Vasculitis may be the primary disease process or complicate an autoimmune

Box 157.4. Autoantibodies Frequently Seen in Systemic Lupus Erythematosus

Autoantibodies (specific)

- Antinuclear
  - Positive in virtually every patient
- Anti-dsDNA
  - Fluctuate with disease activity
  - Increased with active renal disease
- Anti-Smith

Autoantibodies (seen in other disease but associated with a clinical sequelae)

- Coombs—hemolytic anemia
- Anticardiolipin or antiphospholipid—thrombosis, thrombocytopenia, hemolytic anemia
- Anti-ribosomal P—psychiatric disease

Table 157.1. Medications Frequently Used in Pediatric Systemic Lupus Erythematosus

Medication	*Uses*	*Adverse Effects*
NSAIDs	Treatment of arthritis/ arthralgia	Aseptic meningitis (ibuprofen) Gastritis
Corticosteroids	Treatment of skin disease, arthritis/ arthralgia	Poor wound healing Gastritis Osteonecrosis/osteoporosis Weight gain Myopathy Adrenal suppression
Hydroxychloroquine sulfate (eg, Plaquenil, Quineprox)	Prevention of autoantibody formation	Retinopathy
Methotrexate	Treatment of arthritis/ arthralgia	Nausea/vomiting Oral ulcers Hair loss Cytopenias/bone marrow suppression Transaminitis Teratogenesis Methotrexate-induced lung disease
Cyclophosphamide (eg, Cytoxan, Endoxan)	Treatment of refractory SLE nephritis	Cytopenias/bone marrow suppression Hair loss Amenorrhea Infertility Nausea/vomiting
Mycophenolate mofetil (eg, CellCept, Myfortic)	Treatment of SLE nephritis	Fever Hypertension Peripheral edema
Rituximab (eg, Rituxan)	Treatment of autoimmune hemolytic anemia, ITP	Cytopenias/bone marrow suppression
Belimumab (eg, Benlysta)	Treatment of skin disease/ musculoskeletal manifestations	Cytopenias/bone marrow suppression
ACE inhibitors	Treatment of proteinuria/ hypertension	Angioedema Cough

Abbreviations: ACE, angiotensin-converting enzyme; ITP, idiopathic thrombocytopenic purpura; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

disease, infection, or malignancy. Patients with SLE often have vasculitis.

In primary vasculitis, the disease is defined by the size of the affected vessels (Figure 157.1). Small vessel disease includes Henoch-Schönlein purpura (HSP). A small vessel vasculitis associated with granulomas is seen with granulomatosis with polyarteritis (GPA; formerly known as Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome). Medium-sized vessel vasculitides include polyarteritis nodosa, cutaneous polyarteritis, and Kawasaki disease (KD). The large vessels are involved in Takayasu arteritis (Box 157.5).

Epidemiology

The prevalence of vasculitis is estimated to be 23 per 100,000. Henoch-Schönlein purpura and KD are the most common types, but the prevalence is difficult to determine because these diseases are self-limited. Childhood vasculitis occurs in individuals of all ethnic backgrounds. The prevalence of HSP is higher in children of European descent, the prevalence of KD is higher in children of Japanese descent, and the prevalence of Behçet syndrome is higher in children of Turkish ancestry. For HSP, the peak age is 4 to 6 years and boys are affected more frequently, with a female to male ratio of 1:2. Most children with KD are younger than 5 years, and the disease occurs more frequently in boys. The mean age for polyarteritis nodosa is 9 years, and the mean age for GPA is 14 years.

Etiology and Pathogenesis

The etiology of the vasculitides, as with other autoimmune diseases, likely has a genetic and an environmental component. Associations exist with the human leukocyte antigens (HLAs) and a familial inheritance is present, especially in Behçet syndrome (association with HLA-51). Studies have shown a familial link between GPA and rheumatoid arthritis, the association of the α_1-antitrypsin gene (*A1AT*) in GPA, and an association with the familial Mediterranean fever gene (*MEFV*) in Behçet syndrome and HSP.

The pathology includes inflammation of the blood vessels, either in segments or involving the entire vessel. Various degrees of cellular inflammation occur (often polymorphonuclear leukocytes or lymphocytes), along with necrosis in 1 or more layers of the vessel wall.

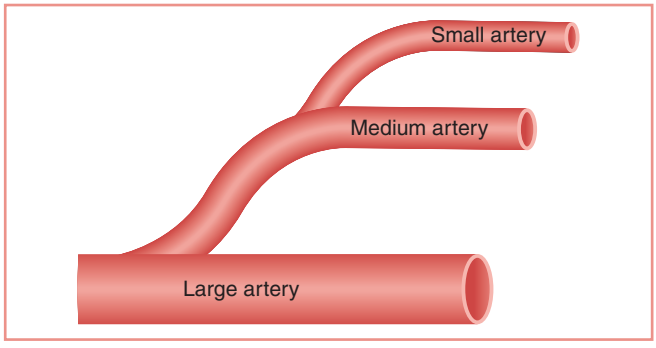

Figure 157.1. Various sized vessels associated with vasculitis.

Box 157.5. Classification and Criteria for Primary Vasculitis

Small Vessel

Henoch Schönlein purpura (IgA immune complex vasculitis)

Criteria[a]

- Purpura or petechiae with lower limb predominance and ≥1 of the 4 following criteria:
  - — Abdominal pain
  - — Histopathology
  - — Arthritis or arthralgia
  - — Renal involvement

ANCA associated vasculitis

Criteria for childhood granulomatosis with polyarteritis (formerly Wegener granulomatosis)[a]

- ≥3 of the 6 following criteria:
  - — Histopathology
  - — Upper airway involvement
  - — Laryngotracheobronchial stenosis
  - — Pulmonary involvement
  - — ANCA positivity
    1. Renal involvement

Medium Vessel

Polyarteritis nodosa

Criteria for childhood type[a]

- Histopathology or angiographic abnormalities plus 1 of the 5 following criteria:
  - — Skin involvement
  - — Myalgia/muscle tenderness
  - — Hypertension
  - — Peripheral neuropathy
  - — Renal involvement

Kawasaki disease

Criteria[b]

- Fever for ≥5 days (high, spiking fevers ≥40°C [≥104°F]) and 4 of the following:
  - — Bilateral conjunctival injection
  - — Mucous membrane changes of the lips and oral cavity
  - — Cervical lymphadenopathy
  - — Polymorphic exanthema
  - — Rash, swelling, and/or induration in the peripheral extremities or perineal area

Large Vessel

Takayasu arteritis

Criteria for childhood type[a]

- Angiographic abnormalities of the aorta or its main branches and pulmonary arteries showing aneurysm/dilatation plus 1 of the 5 following criteria:
  - — Pulse deficit or claudication
  - — Four limbs blood pressure discrepancy
  - — Bruits
  - — Hypertension
  - — Acute phase reactants

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; Ig, immunoglobulin.

[a] Proposed by European League Against Rheumatism, Paediatric Rheumatology INternational Trials Organisation, and Paediatric Rheumatology European Society.

[b] Fewer than 4 criteria are required in the setting of fevers and characteristic coronary artery changes.

Inflammation in the media of a muscular artery tends to destroy the internal elastic lamina. Additional features in some types of vasculitis are giant cells in the vessel wall and the formation of granulomas.

Clinical and Laboratory Presentation and Treatment

Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is an IgA immune complex vasculitis that usually involves lower extremity purpura over the legs and buttocks. The purpura recur as cutaneous purpura "crops" in up to 33% of children, usually associated with running or jumping. Arthritis, usually of the knees and ankles, can be the presenting feature in approximately 50% of children and is present at some point in 75% of children. Lesions resembling cutaneous changes of HSP may be seen in the GI tract and can occur in 50% to 75% of children with HSP. Usually the children experience crampy abdominal pain. Typically, this is limited to bowel wall edema; however, the course may be complicated by bleeding, intussusception, and in severe cases necrosis of the bowel wall. Proteinuria is present in 20% to 60% of children with HSP and is concerning for renal involvement; however, ongoing renal disease is rare, and the risk of chronic renal impairment and end-stage renal disease is 2% to 15% and less than 1%, respectively. Occasionally, HSP can be associated with severe edema over the trunk associated with a low albumin level. Laboratory studies are usually normal, except for occasional increases in the acute phase reactant levels. It is important to test the stool for blood, which is indicative of bowel inflammation. With renal involvement, hematuria or proteinuria may occur. This should be monitored with urine dipstick assessments monthly for 6 months because renal disease may present late and after other clinical symptoms have resolved. Henoch-Schönlein purpura usually self-resolves in less than 1 month but may persist for 3 months. Management of HSP is generally supportive with analgesics and nonsteroidal anti-inflammatory drugs. In children with severe abdominal pain, corticosteroids (oral or, if the child is unable to eat, intravenous [IV] methylprednisolone [1–2 mg/kg per day in divided doses]) is used to prevent ongoing GI inflammation. Generally, HSP resolves and the outcome is good.

Kawasaki Disease

Kawasaki disease involves medium sized blood vessels, is the second most common childhood vasculitis, and can be associated with lifelong cardiac sequelae. Diagnostic criteria are enumerated in Box 157.6.

Box 157.6. Diagnostic Criteria for Kawasaki Disease

- Fever for ≥5 days
- Mucosal changes: strawberry tongue, fissured/erythematous lips, erythematous oropharynx
- Extremity changes: swelling of hands and feet, followed by desquamation and nail changes
- Bilateral conjunctival injection
- Polymorphous rash on the trunk
- Cervical lymphadenopathy (1 node must be >1.5 cm [>0.6 in])

Coronary dilatation and aneurysms may be detected during the acute phase but may develop during the convalescent phase in up to 20% of children, especially in very young children and children of any age for whom treatment was delayed. Multiple organ systems may be involved, including the GI tract (ie, vomiting, abdominal pain, hydrops of the gallbladder), the musculoskeletal system (ie, arthritis), and the CNS. Most of these children are quite irritable, which is suggestive of aseptic meningitis and headache.

Laboratory tests show high levels of acute phase reactants, a high white blood cell count with a shift to the left, and high platelet counts. Antineutrophil cytoplasmic antibodies may be positive as the disease progresses. Early treatment prevents cardiac complications in up to 80% of children.

The American Heart Association recommends treatment with high-dose aspirin (80–100 mg/kg per day) and IV Ig (IVIG; 2 g/kg) within the first 10 days of disease. Aspirin is decreased to an antiplatelet dose of 3 to 5 mg/kg per day after the child is afebrile for 48 hours. If the fever persists or returns, a second course of IVIG is warranted. Infliximab, an anti–tumor necrosis factor (TNF)-α agent (5 mg/kg) is used in some centers if the first dose of IVIG does not resolve the fever. Usually children recover from acute KD, but coronary aneurysms may result in long-term sequelae.

Antineutrophil Cytoplasmic Antibody Vasculitis

The 3 ANCA-associated vasculitides associated with small vessel inflammation are GPA, microscopic polyangiitis, and EGPA. The clinical features of each are enumerated in Table 157.2.

Management of the ANCA-associated vasculitides depends on the severity of the disease. For severe systemic disease, management usually includes a remission induction phase, using cytotoxic therapy (ie, cyclophosphamide) and corticosteroids, followed by a remission maintenance phase, using oral corticosteroids with an oral disease-modifying antirheumatic drug, such as methotrexate or azathioprine. Rituximab has also shown promise as an initial therapy. Some instances of local disease can be managed less aggressively, such as with methotrexate alone. Despite treatment, the rate of relapse is high. Depending on the extent of disease, prognosis is guarded.

Polyarteritis Nodosa

Polyarteritis nodosa is uncommon in children but can be life-threatening. The affected child tends to be ill with fever, malaise, and weight loss complicated by ischemia to involved organs. Often painful subcutaneous nodules develop along affected vessels and aid in the diagnosis. Laboratory findings are consistent with the inflammatory state, and the acute phase reactant levels are high, with a mild leukocytosis and anemia. The perinuclear ANCA may be positive. Corticosteroids are used initially, either oral or IV pulse methylprednisolone. Cyclophosphamide is indicated in severe life- and organ-threatening situations. Plasmapheresis has been shown to be helpful in some cases. Maintenance agents include azathioprine, methotrexate, IVIG, and mycophenolate mofetil (MMF). Recent studies suggest that rituximab may effectively treat this disease. The prognosis is guarded because of the severe organ involvement during the acute phase.

Childhood Primary Central Nervous System Vasculitis

Childhood primary CNS vasculitis may have an acute onset and can include neurologic and/or psychiatric symptoms. Imaging is the mainstay of diagnosis. The 2 types of childhood primary CNS vasculitis are angiography positive, which is seen on MR angiography and affects the medium and large vessels, and angiography negative, which affects the small vessels. To confirm the diagnosis of small vessel disease, angiography is required. Of note, the laboratory studies may be normal peripherally with no clues to the extent

Table 157.2. Antineutrophil Cytoplasmic Antibody–Associated Vasculitides

	Granulomatosis With Polyangiitis	*Microscopic Polyangiitis*	*Eosinophilic Granulomatosis With Polyangiitis*
Organ involvement	Upper/lower respiratory tract, kidneys	Kidneys (capillaritis and necrotizing glomerulonephritis)	Upper/lower respiratory tract, can present as prolonged asthma
Laboratory abnormalities	c-ANCA positive (80%–90% of patients) Elevated ESR/CRP Elevated rheumatoid factor (50% of patients)	p-ANCA positive (75% of patients) Elevated ESR/CRP	p-ANCA positive (<50% of patients) Elevated ESR/CRP Eosinophilia Elevated IgE

Abbreviations: c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; p-ANCA, perinuclear antineutrophil cytoplasmic antibody.

of the CNS vasculitis. The CSF may show increased protein levels or may be normal. Imaging confirms the diagnosis. Therapy includes corticosteroids (oral or IV); however, typically cyclophosphamide is necessary to control the vasculitis. For maintenance therapy, azathioprine or MMF are used for therapeutic control.

Takayasu Arteritis

Takayasu arteritis is a granulomatous vasculitis affecting the large vessels, primarily the aorta and its branches. Diagnosis may be difficult because the symptoms are usually nonspecific. However, clinical clues include absent peripheral pulses, hypertension, CNS symptoms, and claudication. The laboratory tests may be normal, but more often increase of the acute phase reactant levels and anemia are evident. Imaging helps confirm the diagnosis. Corticosteroids are the mainstay of treatment and induce remission in up to 60% of patients. Other treatments include azathioprine, cyclophosphamide, and MMF. Infliximab and other anti-TNF biologics or tocilizumab, an anti-interleukin-6 biologic may be beneficial in these patients. Some of these children go into remission, but the ultimate prognosis depends on the severity of organ involvement during the acute phase.

Inflammatory Myopathies

Juvenile dermatomyositis is the most common pediatric inflammatory myopathy and primarily affects the striated muscles and skin. The prevalence is approximately 3.2 per 1 million children in the United States. Juvenile dermatomyositis is a vasculopathy involving the small arterioles and capillaries of the muscles and skin and results in inflammation and necrosis of muscle fibers. An acute inflammatory phase is associated with proximal muscle weakness. As healing occurs, laying down of calcium (eg, calcinosis) occurs in the areas affected by chronic inflammation. Polymyositis rarely occurs in children but presents in a manner similar to that of JDM, but without skin manifestations and a greater cellular inflammatory response. Myositis may be associated with other connective tissue diseases, such as SLE, mixed connective tissue disease, and scleroderma.

Epidemiology

Although JDM is not common, it is important to recognize the symptoms because early treatment can prevent sequelae. There is a bimodal age range of onset of dermatomyositis; in children the age range of onset is 5 to 14 years, with a peak at 7.6 years; in adults, the age range is 45 to 64 years. Dermatomyositis in adults may be associated with malignancy in up to 20% of patients, but in JDM there is no association with cancer. Juvenile dermatomyositis is more frequent in females, with an overall female to male ratio of 1.7-2.7:1.

Etiology and Pathology

The etiology of JDM is unclear, but several genetic associations are thought to contribute. Associations with both HLA class I, *HLA-B8*, and several class II genes have been found. The TNF-α 308A allele is noted in increased frequency in patients with JDM and is associated with the increased production of TNF-α that perpetuates the inflammatory response. In these susceptible individuals, infectious agents may increase the risk of inflammation. Often, an upper respiratory infection or GI illness precedes the onset of JDM. Infections, including coxsackievirus, influenza, group A streptococcus, toxoplasmosis, parvovirus, hepatitis B, *Borrelia,* and Leishmania, have been reported in association with JDM. Additionally, JDM has been reported after vaccinations. Several studies suggest that JDM may be a result of microchimerism, in which the mother's cells are present in the child's muscle tissue, resulting in an immune response.

The pathogenesis is that of an autoimmune vasculopathy with an immune attack on muscle arterioles, capillaries, and endothelium that results in vascular damage and vessel occlusion. Additionally, deposition of immune complexes may occur that contribute to vascular injury. The skin and muscle, primarily the striated muscles but also muscles of the GI tract, are involved. Muscle fibers near the affected vessels demonstrate atrophy or necrosis.

Clinical Presentation

The criteria in Box 157.7 are useful in making a diagnosis of JDM. These criteria have not been validated, however.

Muscle Involvement

Often, the child with JDM has an insidious progression over 3 to 6 months of malaise, low-grade fevers, and fatigue. Muscle pain or tenderness occurs in 25% to 75% of these patients, and edema over the affected muscles may be present. The predominant feature is proximal muscle weakness of the neck, abdominal muscles, and limb girdles. On examination, the child is unable to sit up from the supine position without rolling over and using the arms to push up into a sitting position, to rise from sitting to standing, or to squat or sit on the floor and get up without help. On getting up from the floor, the Gowers sign is often present, and on walking the child may exhibit a truncal sway and a positive Trendelenburg gait indicative of weakness of the hips.

Box 157.7. Criteria for the Diagnosis of Juvenile Dermatomyositis

- Symmetric proximal muscle weakness
- Characteristic cutaneous changes
  - Heliotrope rash: discoloration of the eyelids with periorbital edema
  - Gottron papules: erythematous, scaly rash over dorsal aspects of the metacarpal and proximal interphalangeal joints
- Elevated skeletal muscle enzymes: creatine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, aldolase
- Electromyographic evidence of myopathy and denervation
- Muscle biopsy demonstrating necrosis and inflammation

Derived from Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med.* 1975;292(7):344–347; and Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med.* 1975;292(8):403–407.

Pharyngeal, hypopharyngeal, and palatal muscles can be affected, and such involvement must be recognized promptly to prevent aspiration or respiratory distress. It is important to evaluate this urgently with a barium swallow and PFTs.

Skin Involvement

More than 75% of children have cutaneous abnormalities that are pathognomonic of the disease at presentation. Cutaneous manifestations usually present at diagnosis and include the heliotrope discoloration around the eyes and edema of the eyelids. Other findings include *Gottron papules*—shiny, erythematous, scaly plaques that are symmetric over the proximal interphalangeal and metacarpophalangeal joints of the hand, extensor surfaces of the elbows and knees, and, more rarely, malleoli of the ankles. The findings result from the vasculopathy and subsequent ischemia. Less frequently appreciated but usually present is the inflammation and erythema of periungual skin and capillary nail bed that often show the presence of dilatation of vessel loops, thrombosis and hemorrhage, and, ultimately, loss of the capillary nail bed vessels. *Lipodystrophy* (ie, loss of fat from the body and extremities or local fat loss) occurs in 7% to 50% of affected children and can be associated with other metabolic problems.

Ulceration related to ischemic changes may occur. In the anatomic areas of chronic inflammation, calcification occurs in 12% to 43% of patients, sometimes within 6 months of onset. Calcification may occur in the skin or muscle belly or diffusely and is problematic because of recurrent skin ulcerations, limitation of motion, pain in the involved muscle, and increased risk of infection because of poor skin integrity. Management of calcinosis is difficult and may require surgical removal in some instances.

Gastrointestinal Involvement

The muscles of the GI tract may also be involved with inflammation throughout the bowel and microperforations when the disease is active. The child presents with progressive abdominal pain, melena, and hematemesis, or an ileus. Imaging studies may show free intraperitoneal air, but because the perforations are multiple and small, often no free air is noted radiographically. This is a medical emergency, and the affected child should be treated for sepsis and evaluated for possible surgical intervention.

Cardiovascular Involvement

Cardiac involvement is rare but may be life threatening. Myocarditis, conduction defects, or first-degree heart block may be delayed in presentation but can cause death. Hypertension can occur in 25% to 50% of patients, especially with glucocorticoid therapy. Prior to any surgery, the child with JDM should undergo a careful cardiac evaluation to ensure they are able to tolerate the procedure.

Involvement of Other Systems

Arthritis and arthralgia are frequent complications of JDM and may occur in 10% to 65% of children with the disease. Lymphadenopathy occurs early in the disease course in 10% to 65% of children and usually improves with treatment.

Laboratory Studies

Laboratory studies, including a complete blood cell count and inflammatory markers (ie, erythrocyte sedimentation rate, C-reactive protein), may be normal, but in the setting of marked inflammation in the skin and muscle the inflammatory markers may be elevated. Leukocytosis and anemia are rare except in the child with infection or GI bleeding. Urinalysis is usually normal. Because of the vasculopathy, factor VIII-related antigen (ie, von Willebrand factor) may be high in the child with active disease. Flow cytometry studies show increased numbers of $CD19^+$ B cells.

Muscle Enzymes

Serum levels of the sarcoplasmic muscle enzymes (ie, aspartate transaminase, creatine kinase, lactate dehydrogenase, aldolase) contribute to making the diagnosis and monitoring the effectiveness of therapy. Aspartate transaminase and lactate dehydrogenase correlate the best with active disease. Usually, creatine kinase level is elevated, but it may fluctuate and is the first to decrease with therapy. The other enzymes may remain high and decrease more slowly as the disease improves.

Autoantibodies

The ANA is positive in 10% to 85% of patients, and antibodies against small RNA antigens (ie, RNP, SS-A/SS-B) may be present. Traditional myositis-specific autoantibodies are rare in JDM, although anti-Jo-1 antibodies are seen in 2% to 5% of children with JDM, especially those with severe Raynaud disease and interstitial lung disease. Anti-Mi-2 is seen in 1% to 7% of those with milder disease. More recently, myositis specific autoantibodies have been associated with disease manifestations and commercial panels are now available. For example, anti-transcription intermediary factor 1-g autoantibodies (anti-p155) are associated with more severe cutaneous involvement and lipodystrophy and in adults increased cancer risk. Anti-nuclear matrix protein-2 autoantibodies (anti-p140) are associated with calcinosis and contractures and are identified in 13% to 29% of children with JDM. Anti-melanoma differentiation-associated protein 5 antibodies are associated with unique mucocutaneous features, severe lung disease, and minimal muscle involvement. The anti-signal recognition particle autoantibody level may be a clinically useful marker of disease activity.

Imaging Studies

Radiographs may show muscle edema and osteoporosis, but to determine the extent of muscle edema, MR imaging, especially the fat-suppressed T2-weighted or short T1 inversion recovery sequences, is required. Short T1 inversion recovery is optimal to show hyperintensity indicating muscle edema.

Electromyography and Muscle Biopsy

Electromyography showing a myopathic pattern and muscle biopsy with inflammation and loss of muscle fibers are rarely needed for the diagnosis. Usually, these are used in cases that are unclear and for which another criterion for diagnosis is needed.

Treatment

The use of corticosteroids has changed the prognosis for children with JDM. Corticosteroids decrease inflammation, improve skin manifestations and muscle strength, and prevent the chronic inflammation that results in calcinosis. Almost all children require corticosteroid therapy; if they have more severe disease, a methylprednisolone sodium succinate pulse (30 mg/kg with a maximum of 1 gm each day for 3 days) or a daily oral prednisone dose of 2 mg/kg is the first-line treatment. As strength improves and muscle enzymes return to normal, steroids are tapered. An adverse event of note with the use of corticosteroids is the onset of steroid-induced myopathy. However, in this case, muscle enzymes are not elevated. If the response to steroids is inadequate, methotrexate is generally the second-line treatment, and if this is not sufficiently effective, IVIG is used. Hydroxychloroquine is useful for skin manifestations and may decrease the risk of calcinosis. Immunosuppressants may be necessary to manage vasculopathy of the bowel or other organs. For severe involvement, cyclophosphamide is indicated, but in less severe cases, azathioprine or cyclosporine is used. More recently, rituximab has been found to reverse severe muscle disease. Most children with JDM benefit from physical therapy. It is important to protect the skin from ultraviolet light and prevent tissue injury. A proper diet and physical activity are important to promote optimal intake of calcium and vitamin D and prevent osteopenia, muscle atrophy, and contractures.

Scleroderma: Systemic Sclerosis, Localized Scleroderma, and Morphea

Scleroderma means "hard skin," and patients with this disease have increased skin thickening that can be systemic or localized. The current terminology classifies the systemic disease by the extent of the skin involvement into 2 categories: diffuse cutaneous systemic sclerosis (dSSc) and limited cutaneous systemic sclerosis (lSSc), which was previously called CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia). The localized scleroderma (LS) type includes morphea and linear scleroderma.

Epidemiology

Worldwide reports of dSSc exist with an annual incidence of 0.45 to 1.9 per 100,000 and a prevalence of 24 per 100,000. The disease is more common in African Americans and Choctaw Native Americans. The systemic form of the disease is rare in children, who comprise only approximately 1.2% to 9% of all cases. Morphea and linear scleroderma are seen predominantly in the pediatric population, with 67% of cases diagnosed before 18 years of age. The prevalence of morphea in children younger than 17 years is estimated to be 50 per 100,000. The prevalence of LS is approximately 2.7 cases per 100,000. Females are affected more often than males.

Etiology and Pathogenesis

Much remains to be learned about the scleroderma spectrum. The skin thickening is believed to be caused by a dysfunction of the immune system that activates the endothelium and fibroblasts that promote fibrosis. The genetic influence is not clear, but association exists with certain HLA markers. This is believed to be an autoimmune process because of the disease-specific autoantibodies and multiple abnormalities of T cell function (eg, cellular immunity) with increased cytokines, adhesion molecules, and growth factors resulting in endothelial injury and fibroblast proliferation. The signs and symptoms mimic graft-versus-host disease, with abnormalities of regulation of fibroblasts, production of collagen, and immunologic abnormalities. Some studies suggest microchimerism may play a role in the pathogenesis of the sclerodermas, as well as in the pathogenesis of dermatomyositis.

Clinical Manifestations

Systemic Sclerosis

The Pediatric Rheumatology European Society, American College of Rheumatology, and European League Against Rheumatism developed criteria useful in diagnosis and research. Juvenile systemic sclerosis involves children younger than 16 years with 1 major criterion (presence of skin sclerosis/induration proximal to metacarpophalangeal joints) and at least 2 of the 20 minor criteria (Box 157.8).

Because early on the course and progression of dSSc and lSSc may be insidious, the diagnosis may not be made for several years after the condition has had a significant effect on function or mobility. The characteristic presentation is a child with Raynaud phenomenon; tightening, thinning, and atrophy of the skin of the hands and face; or the appearance of cutaneous telangiectasias about the face, upper trunk, and hands. At the onset, edema of the skin may occur that persists for a few weeks or months, and this may offer a window of opportunity for treatment to decrease the inflammation and the resulting fibrosis. The next phase is the sclerotic phase, in which sclerosis is noticeable especially over the digits (ie, acrosclerosis, sclerodactyly) and face (ie, circumoral furrowing). Finally, atrophy of the skin occurs. Telangiectasia and calcinosis may be noted during this process. Arthritis may be a symptom in approximately 36% of children. Radiographs may show resorption of the distal tufts of the digits.

The greatest morbidity is related to involvement of the cardiovascular, pulmonary, renal, and GI systems. Pericardial effusions may be the initial presentation, but morbidity is from cardiac ischemia of the coronary arteries and cardiac fibrosis. Systemic hypertension may be a complication and must be monitored carefully, especially because it may be indicative of renal crisis. Pulmonary parenchymal disease often is asymptomatic early, but a patient may exhibit symptoms of a dry cough or dyspnea on exertion. The patient may eventually develop interstitial pneumonitis or pulmonary hypertension with significant morbidity and mortality. Pulmonary complications can be monitored by high-resolution chest CT and pulmonary PFTs. Renal disease is also an ominous complication of dSSc. A database of children with dSSc noted that 5% had renal involvement and 1% developed renal crisis. The presence of anti-topoisomerase and/or anti-RNA polymerase antibodies and rapidly progressing skin involvement are thought to be predictors of renal and cardiac involvement. Concern among rheumatologists caring for adults is the relationship between the use of high-dose steroids and the

Box 157.8. Criteria for Juvenile Systemic Sclerosis

Major Criterion

- Sclerosis/induration of the skin proximal to the metacarpophalangeal or metatarsophalangeal joints

Minor Criteria

Skin
- Sclerodactyly

Vasculopathy
- Raynaud phenomenon
- Nail fold capillary abnormalities
- Digital tip ulcers

Gastrointestinal
- Dysphagia
- Gastroesophageal reflux

Renal
- Renal crisis
- New-onset arterial hypertension

Cardiac
- Arrhythmias
- Heart failure

Respiratory
- Pulmonary fibrosis (high-resolution computed tomography/radiography)
- Decreased diffusion lung capacity for carbon monoxide
- Pulmonary hypertension

Musculoskeletal
- Tendon friction rubs
- Arthritis
- Myositis

Neurologic
- Neuropathy
- Carpal tunnel syndrome

Serology
- Antinuclear antibodies
- Systemic sclerosis selective autoantibodies (anti-centromere, anti-topoisomerase 1, anti-fibrillarin, anti-polymyositis-scleroderma, anti-fibrillin, or anti-RNA polymerase 1 or 3)

Adapted with permission from Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League Against Rheumatism provisional classification criteria for juvenile systemic sclerosis. *Arthritis Rheum.* 2007;57(2):203–212.

development of scleroderma renal crisis; thus, corticosteroids to reverse skin involvement must be used with caution and close monitoring is necessary. Gastrointestinal involvement is common, affecting one-third of patients during the disease. The oral cavity may have telangiectasia, and often patients report dry mouth or the sicca syndrome. Esophageal involvement may present early in the disease with heartburn and delayed gastric emptying that can result in aspiration. The small bowel is often involved with decreased motility and malabsorption and the large bowel with constipation.

Localized Scleroderma

The Pediatric Rheumatology European Society proposed a classification system for LS with 5 subtypes: circumscribed morphea, linear scleroderma, generalized morphea, pansclerotic morphea, and mixed morphea, in which a combination of 2 or more of the previous subtypes is present (Box 157.9).

Linear scleroderma is the most common subtype in children and adolescents, characterized by 1 or more linear streaks that typically involve an upper or lower extremity. With time, the streaks become progressively more indurated and can extend through the dermis, subcutaneous tissue, and muscle to the underlying bone. En coup de sabre involves the scalp and head and was named as such because it once was thought to look like the depression caused by the strike from a sword; progressive facial hemiatrophy may occur. Parry-Romberg syndrome is characterized by progressive facial hemiatrophy of the skin and tissue below the forehead. The patient with facial hemiatrophy may experience associated seizures and dental and ocular abnormalities.

Morphea, or areas of indurated, waxy skin with an ivory center and violaceous halo, are most commonly found on the trunk. The lesions may be small (<1 cm [<0.4 in]) and are called guttate or larger and may become confluent or generalized morphea. Deep morphea, in which the entire skin is thickened and feels bound down, includes subcutaneous morphea and eosinophilic fasciitis. This form is the least common and is considered the most disabling. Although LS involves primarily the skin, some patients develop musculoskeletal problems.

Laboratory Studies

In systemic sclerosis, the complete blood cell count shows anemia in approximately 25% of patients and may reflect anemia of chronic disease or may be caused by vitamin B_{12} or folate deficiency resulting from chronic malabsorption. Leukocytosis is rare, but eosinophilia occurs in approximately 15% of patients. Generally, these laboratory results are normal in localized scleroderma.

Autoantibodies

High titers of ANAs in the speckled pattern are frequently seen in approximately 80% of patients with systemic sclerosis. Anti-topoisomerase 1 (anti-sclerosis-70) autoantibodies are present in

Box 157.9. Classification of Juvenile Localized Scleroderma

1. Circumscribed morphea: round circumscribed areas
2. Linear scleroderma: affecting the trunk or limb, the head (en coup de sabre ["blow of a saber"]); Parry-Romberg syndrome or progressive facial hemiatrophy
3. Generalized morphea: induration of the skin that becomes confluent, eventually involving a large area
4. Pansclerotic morphea: circumferential involvement of limb(s) affecting the skin, subcutaneous tissue, muscle, and bone
5. Mixed morphea: combination of 2 or more of the previous subtypes

Reprinted with permission from Laxer RM, Zulian F. Localized scleroderma. *Curr Opin Rheumatol.* 2006;18(6):606–613.

28% to 34% of patients and are usually seen in patients with dSSc with peripheral vascular disease, digital pitting, pulmonary interstitial fibrosis, renal involvement, and higher rate of mortality. Anticentromere antibodies occur almost exclusively in patients with lSSc in association with calcinosis and telangiectasias; they are seen less frequently in children. The anti-RNA polymerase III antibodies are associated with rapidly progressive skin disease and renal crisis.

In LS, ANAs are present in 23% to 73% of patients but are not predictive of the disease course. Anti-histone antibodies are detected in 47% of patients, are associated with more extensive localized disease, and may be useful in assessing disease activity.

Treatment

Treatment remains problematic for dSSc and lcSSc, and often, patients do not respond to therapies. Raynaud phenomenon and digital ulcers are managed with calcium channel blockers and sildenafil citrate. More recently, iloprost (synthetic analogue of prostacyclin prostaglandin I2) and competitive antagonists of endothelin-1 A, B (bosentan, macitentan) are used for severe digital ulcers. Iloprost and the endothelin inhibitors are useful in pulmonary hypertension to increase vascular dilatation and decrease pulmonary vascular resistance. To decrease inflammation in the lung, cyclophosphamide may be used in severe cases and other immunosuppression drugs (MMF or azathioprine) and hydroxychloroquine in more mild cases. Angiotensin-converting enzyme inhibitors play an important role in preventing renal crisis. In some cases, the skin disease is managed cautiously with low-dose steroids early in the disease during the edematous phase and with methotrexate during the sclerotic phase. Gastroesophageal reflux disease is managed with proton pump inhibitors. Supportive care is of great importance with attention to skin integrity, joint range of motion, and GI issues with weight loss. It is necessary for the physician to educate the family and child on the disease and its complications. The physician should inform the school of the child's potential needs while at school and any limitations. In addition, the physician can serve as a resource and source of information about dSSc and lcSSc for the community. Despite all treatment efforts, the prognosis is guarded.

Protocols have been proposed for the therapy of LS that include treatment with methotrexate in combination with corticosteroids. Linear scleroderma should be addressed early because it tends toward a progressive process. If lesions do not improve or if they expand, MMF is useful to inhibit further fibrosis. The difficulty in measuring lesion size makes it difficult to fully assess response to treatment.

Prognosis

Prognosis is improving for most autoimmune diseases because of the increased understanding of the pathogenesis. Criteria are being established and validated to aid in the diagnosis of each disease and optimize treatment. Consultation with rheumatologists, neurologists, nephrologists, and infectious disease specialists may be necessary to assist in the final diagnosis.

The care of a child with an autoimmune disease requires a multidisciplinary approach involving a primary care physician, rheumatologist, and subspecialists with expertise in affected target organs. The role of the primary care physician is to ensure routine care of the patient as well as prevent long-term sequelae of the disease and its treatment. Because many of the agents used to manage autoimmune disease have significant side effects, it is vital for the primary care physician to have a thorough understanding of the patient's medication regimen. The patient with autoimmune disease often experiences growth failure from the disease process or its treatment. Ensuring appropriate diet and physical activity is vital. Supplementation with calcium and vitamin D is beneficial to prevent osteoporosis. Periodic ophthalmologic screening, which is essential to assess for disease activity or adverse effects from medication, should be done at least annually. In the long term, the patient with autoimmune disease is at increased risk for cardiovascular disease secondary to chronic inflammation. An annual cardiovascular risk assessment may be required that includes a review of the diet and lipid profiles. The individual who has sustained a thrombolytic event or is at high risk for thrombosis may benefit from low-dose aspirin prophylaxis. As with any patient with a chronic disease, consideration of quality of life is essential. Disease management for the patient with autoimmune disease is a balance of optimal function, minimal complications, and improved quality of life.

CASE RESOLUTION

Initially criteria were insufficient for a diagnosis of SLE (ie, rashes, but not clarified if photosensitive; swelling and hypertension suggestive of renal disease; arthritis); however, it is clear that the adolescent has findings consistent with SLE. Additional questions about the history reveal that the sun made the girl's rashes worse, she had mouth sores, in the morning her eyes were puffy, and she sometimes had chest pain and trouble breathing. On physical examination, she was found to have a malar rash and a rash on the hard palate with other mouth sores, pitting edema of her feet and ankles, and mild hypertension. Laboratory results showed a mild anemia and lymphopenia, an ANA of 1:320 in a homogenous pattern, positive anti-ds-DNA antibodies, and low C3 (normal range: 87–158 mg/dL) and low C4 (normal range: 14–36 mg/dL). The urinalysis had 3+ protein and the protein/creatinine ratio was 1.0 (normal range: 0–0.4). With these additional findings the girl meets the criteria for a diagnosis of SLE with lupus nephritis. She is referred to a pediatric rheumatologist and nephrologist, and lupus nephritis (class III) is confirmed on renal biopsy. The girl is started on treatment with steroids and immunosuppression and improves over the next 6 months.

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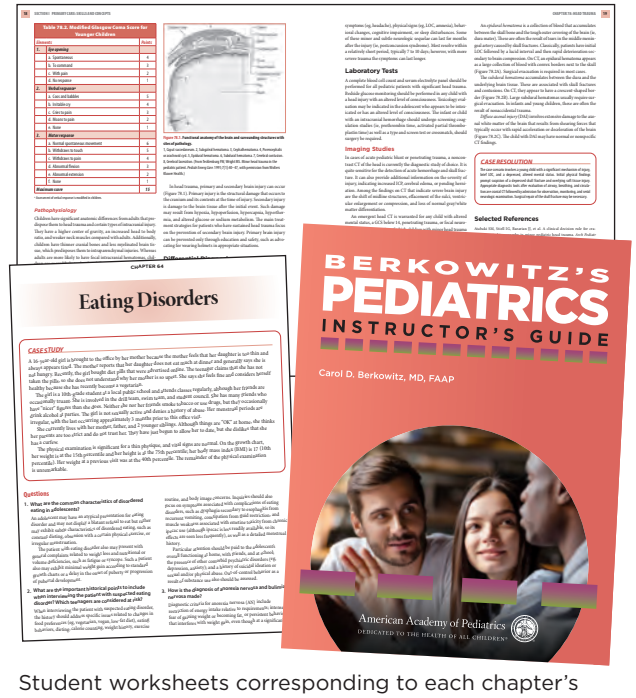

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